TITLE OF THE INVENTION

MU-CONOPEPTIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a division of U.S. patent application Serial No. 09/910,009 filed on 23 July 2001. The present application is also related to and claims benefit under 35 USC §119(e) to U.S. provisional patent applications Serial No. 60/219,619 filed on 21 July 2000, Serial No. 60/245,157 filed on 3 November 2000, Serial No. 60/264,319 filed on 29 January 2001 and Serial No. 60/277,270 filed on 21 March 2001. Each of these applications is incorporated herein by reference.

[0002] This invention was made with Government support under Grant No. PO1 GM48677 awarded by the National Institute of General Medical Sciences, National Institutes of Health, Bethesda, Maryland. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] The present invention is to μ-conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated sodium channels. Thus, the μ-conopeptides or derivatives are useful as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ-conopeptides are also useful for treating neuromuscular disorders. The invention is further directed to nucleic acid sequences encoding the μ-conopeptides and encoding propeptides, as well as the propeptides.

[0004] The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference, and for convenience are referenced in the following text by author and date and are listed alphabetically by author in the appended bibliography.

[0005] *Conus* is a genus of predatory marine gastropods (snails) which envenomate their prey. Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as *Conus magus* the cone detects the presence of the fish using chemosensors in its siphon and when close enough extends its proboscis and fires a hollow harpoon-like tooth containing venom into the fish. This

immobilizes the fish and enables the cone snail to wind it into its mouth via an attached filament. For general information on *Conus* and their venom see the web address grimwade.biochem.unimelb. edu.au/cone/referenc.html. Prey capture is accomplished through a sophisticated arsenal of peptides which target specific ion channel and receptor subtypes. Each *Conus* species venom appears to contain a unique set of 50-200 peptides. The composition of the venom differs greatly between species and between individual snails within each species, each optimally evolved to paralyze its prey. The active components of the venom are small peptides toxins, typically 10-40 amino acid residues in length and are typically highly constrained peptides due to their high density of disulphide bonds.

[0006] The venoms consist of a large number of different peptide components that when separated exhibit a range of biological activities: when injected into mice they elicit a range of physiological responses from shaking to depression. The paralytic components of the venom that have been the focus of recent investigation are the α-, ω- and μ-conotoxins. All of these conotoxins act by preventing neuronal communication, but each targets a different aspect of the process to achieve this. The α-conotoxins target nicotinic ligand gated channels, the μ-conotoxins target the voltage-gated sodium channels and the ω-conotoxins target the voltage-gated calcium channels (Olivera et al., 1985; Olivera et al., 1990). For example a linkage has been established between α-, αA- & ψ-conotoxins and the nicotinic ligand-gated ion channel; ω-conotoxins and the voltage-gated calcium channel; μ-conotoxins and the voltage-gated sodium channel; δ-conotoxins and the voltage-gated sodium channel; κ-conotoxins and the voltage-gated potassium channel; conantokins and the ligand-gated glutamate (NMDA) channel.

[0007] However, the structure and function of only a small minority of these peptides have been determined to date. For peptides where function has been determined, three classes of targets have been elucidated: voltage-gated ion channels; ligand-gated ion channels, and G-protein-linked receptors.

[0008] *Conus* peptides which target voltage-gated ion channels include those that delay the inactivation of sodium channels, as well as blockers specific for sodium channels, calcium channels and potassium channels. Peptides that target ligand-gated ion channels include antagonists of NMDA and serotonin receptors, as well as competitive and noncompetitive nicotinic receptor antagonists. Peptides which act on G-protein receptors include neurotensin and vasopressin receptor agonists. The unprecedented pharmaceutical selectivity of conotoxins

is at least in part defined by a specific disulfide bond frameworks combined with hypervariable amino acids within disulfide loops (for a review see McIntosh et al., 1998).

[0009] There are drugs used in the treatment of pain, which are known in the literature and to the skilled artisan. See, for example, Merck Manual, 16th Ed. (1992). However, there is a demand for more active analgesic agents with diminished side effects and toxicity and which are non-addictive. The ideal analgesic would reduce the awareness of pain, produce analgesia over a wide range of pain types, act satisfactorily whether given orally or parenterally, produce minimal or no side effects, be free from tendency to produce tolerance and drug dependence.

[0010] Due to the high potency and exquisite selectivity of the conopeptides, several are in various stages of clinical development for treatment of human disorders. For example, two *Conus* peptides are being developed for the treatment of pain. The most advanced is ω-conotoxin MVIIA (ziconotide), an N-type calcium channel blocker (see Heading, C., 1999; U.S. Patent No. 5,859,186). ω-Conotoxin MVIIA, isolated from *Conus magus*, is approximately 1000 times more potent than morphine, yet does not produce the tolerance or addictive properties of opiates. ω-Conotoxin MVIIA has completed Phase III (final stages) of human clinical trials and has been approved as a therapeutic agent. ω-Conotoxin MVIIA is introduced into human patients by means of an implantable, programmable pump with a catheter threaded into the intrathecal space. Preclinical testing for use in post-surgical pain is being carried out on another *Conus* peptide, contulakin-G, isolated from *Conus geographus* (Craig et al. 1999). Contulakin-G is a 16 amino acid O-linked glycopeptide whose C-terminus resembles neurotensin. It is an agonist of neurotensin receptors, but appears significantly more potent than neurotensin in inhibiting pain in *in vivo* assays.

[0011] In view of a large number of biologically active substances in *Conus* species it is desirable to further characterize them and to identify peptides capable of treating disorders involving voltage gated ion channels, such as stroke and pain. Surprisingly, and in accordance with this invention, Applicants have discovered novel conotoxins that can be useful for the treatment of disorders involving voltage gated ion channels and could address a long felt need for a safe and effective treatment.

SUMMARY OF THE INVENTION

[0012] The present invention is to μ-conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives

thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated with voltage-gated sodium channels. Thus, the μ-conopeptides or derivatives are useful as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ-conopeptides are also useful for treating neuromuscular disorders. The invention is further directed to nucleic acid sequences encoding the μ-conopeptides and encoding propeptides, as well as the propeptides.

[0013] More specifically, the present invention is directed to μ-conopeptides, having the amino acid sequences set forth in Tables 1 and 2 below.

[0014] The present invention is also directed to derivatives or pharmaceutically acceptable salts of the μ-conopeptides or the derivatives. Examples of derivatives include peptides in which the Arg residues may be substituted by Lys, ornithine, homoargine, nor-Lys, N-methyl-Lys, N,N-dimethyl-Lys, N,N,N-trimethyl-Lys or any synthetic basic amino acid; the Lys residues may be substituted by Arg, ornithine, homoargine, nor-Lys, or any synthetic basic amino acid; the Tyr residues may be substituted with meta-Tyr, ortho-Tyr, nor-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, nitro-Tyr or any synthetic hydroxy containing amino acid; the Ser residues may be substituted with Thr or any synthetic hydroxylated amino acid; the Thr residues may be substituted with Ser or any synthetic hydroxylated amino acid; the Phe residues may be substituted with any synthetic aromatic amino acid; the Trp residues may be substituted with Trp (D), neo-Trp, halo-Trp (D or L) or any aromatic synthetic amino acid; and the Asn, Ser, Thr or Hyp residues may be glycosylated. The halogen may be iodo, chloro, fluoro or bromo; preferably iodo for halogen substituted-Tyr and bromo for halogen-substituted Trp. The Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho-derivatives. The acidic amino acid residues may be substituted with any synthetic acidic amino acid, e.g., tetrazolyl derivatives of Gly and Ala. The aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side chains C_nH_{2n+2} up to and including n=8. The Met residues may be substituted by norleucine (Nle). The Cys residues may be in D or L configuration and may optionally be substituted with homocysteine (D or L).

[0015] Examples of synthetic aromatic amino acid include, but are not limited to, nitro-Phe, 4-substituted-Phe wherein the substituent is C_1-C_3 alkyl, carboxyl, hyrdroxymethyl, sulphomethyl, halo, phenyl, -CHO, -CN, -SO_3H and -NHAc. Examples of synthetic hydroxy containing amino acid, include, but are not limited to, such as 4-hydroxymethyl-Phe, 4-

hydroxyphenyl-Gly, 2,6-dimethyl-Tyr and 5-amino-Tyr. Examples of synthetic basic amino acids include, but are not limited to, N-1-(2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl)-Gly and 2-[3-(2S)pyrrolininyl)-Ala. These and other synthetic basic amino acids, synthetic hydroxy containing amino acids or synthetic aromatic amino acids are described in Building Block Index, Version 3.0 (1999 Catalog, pages 4-47 for hydroxy containing amino acids and aromatic amino acids and pages 66-87 for basic amino acids; see also web address amino-acids. com), incorporated herein by reference, by and available from RSP Amino Acid Analogues, Inc., Worcester, MA. Examples of synthetic acid amino acids include those derivatives bearing acidic functionality, including carboxyl, phosphate, sulfonate and synthetic tetrazolyl derivatives such as described by Ornstein et al. (1993) and in U.S. Patent No. 5,331,001, each incorporated herein by reference.

[0016] Optionally, in the μ-conopeptides of the present invention, the Asn residues may be modified to contain an N-glycan and the Ser, Thr and Hyp residues may be modified to contain an O-glycan (e.g., g-N, g-S, g-T and g-Hyp). In accordance with the present invention, a glycan shall mean any N-, S- or O-linked mono-, di-, tri-, poly- or oligosaccharide that can be attached to any hydroxy, amino or thiol group of natural or modified amino acids by synthetic or enzymatic methodologies known in the art. The monosaccharides making up the glycan can include D-allose, D-altrose, D-glucose, D-mannose, D-gulose, D-idose, D-galactose, D-talose, D-galactosamine, D-glucosamine, D-N-acetyl-glucosamine (GlcNAc), D-N-acetyl-galactosamine (GalNAc), D-fucose or D-arabinose. These saccharides may be structurally modified, e.g., with one or more O-sulfate, O-phosphate, O-acetyl or acidic groups, such as sialic acid, including combinations thereof. The gylcan may also include similar polyhydroxy groups, such as D-penicillamine 2,5 and halogenated derivatives thereof or polypropylene glycol derivatives. The glycosidic linkage is beta and 1-4 or 1-3, preferably 1-3. The linkage between the glycan and the amino acid may be alpha or beta, preferably alpha and is 1-.

[0017] Core O-glycans have been described by Van de Steen et al. (1998), incorporated herein by reference. Mucin type O-linked oligosaccharides are attached to Ser or Thr (or other hydroxylated residues of the present peptides) by a GalNAc residue. The monosaccharide building blocks and the linkage attached to this first GalNAc residue define the "core glycans," of which eight have been identified. The type of glycosidic linkage (orientation and connectivities) are defined for each core glycan. Suitable glycans and glycan analogs are described further in U.S. Serial No. 09/420,797 filed 19 October 1999 (now U.S. Patent No.

6,369,193) and in PCT Application No. PCT/US99/24380 filed 19 October 1999 (PCT Published Application No. WO 00/23092), each incorporated herein by reference. A preferred glycan is Gal(β1→3)GalNAc(α1→).

[0018] Optionally, in the μ-conopeptides described above, pairs of Cys residues may be replaced pairwise with isoteric lactam or ester-thioether replacements, such as Ser/(Glu or Asp), Lys/(Glu or Asp), Cys/(Glu or Asp) or Cys/Ala combinations. Sequential coupling by known methods (Barnay et al., 2000; Hruby et al., 1994; Bitan et al., 1997) allows replacement of native Cys bridges with lactam bridges. Thioether analogs may be readily synthesized using halo-Ala residues commercially available from RSP Amino Acid Analogues.

[0019] The present invention is further directed to derivatives of the above peptides and peptide derivatives which are acylic permutations in which the cyclic permutants retain the native bridging pattern of native toxin. See, for example, Craik et al. (2001).

[0020] The present invention is further directed to a method of treating disorders associated with voltage gated ion channel disorders in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. The present invention is also directed to a pharmaceutical composition comprising a therapeutically effective amount of a μ-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier.

[0021] More specifically, the present invention is further directed to uses of these peptides or nucleic acids as described herein as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ-conopeptides are also useful for treating neuromuscular disorders.

[0022] The present invention is directed to the use of μ-conopeptides as a local anesthetic for treating pain. The μ-conopeptides have long lasting anesthetic activity and are particularly useful for spinal anesthesia, either administered acutely for post-operative pain or via an intrathecal pump for severe chronic pain situations. The μ-conopeptides are also useful as analgesics in chronic and neuropathic pain states, such as trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, neuroma pain and phantom limb pain. The μ-conopeptides are also useful for treating burn pain and as ocular anesthetics.

[0023] The present invention is directed to the use of μ-conopeptides as neuroprotectants. The μ-conopeptides are useful for the treatment and alleviation of epilepsy and as a general

anticonvulsant agent. The μ-conopeptides are also useful for treating neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS). The μ-conopeptides are further useful as cerebroprotectants, such as for reducing neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events.

[0024] The present invention is directed to the use of μ-conopeptides as neuromuscular blockers and for treating neuromuscular disorders. As such, the μ-conopeptides are useful for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use.

[0025] More specifically, the present invention is also directed to nucleic acids which encode μ-conopeptides of the present invention or which encodes precursor peptides for these μ-conopeptides, as well as the precursor peptide. The nucleic acid sequences encoding the precursor peptides of other μ-conopeptides of the present invention are set forth in Table 1. Table 1 also sets forth the amino acid sequences of these precursor peptides.

[0026] The present invention is further directed to the use of selectively radioiodinated or radiotritiated μ-conopeptides for characterizing pore occlusion sites on different sodium channel subtypes or for use in screening assays.

[0027] The present invention is also directed to the use of μ-conopeptides for screening small molecule libraries to identify small molecules that are selective blocking agents at specific sodium channel subtypes expressed in mammalian systems. In one embodiment, the blocking activity of a small molecule at a particular sodium channel subtype is compared to the blocking activity of a μ-conopeptide at the same sodium channel subtype. In a second embodiment, the ability of a small molecule to displace a μ-conopeptide from a sodium channel subtype is determined. In a third emdiment, the binding affinity of a small molecule for a sodium channel subtype is compared to the binding affinity of a μ-conopeptide for the same sodium channel subtype.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0028] The present invention is to μ-conopeptides, derivatives or pharmaceutically acceptable salts thereof. The present invention is further directed to the use of this peptide, derivatives thereof and pharmaceutically acceptable salts thereof for the treatment of disorders associated

with voltage-gated sodium channels. Thus, the μ-conopeptides or derivatives are useful as neuromuscular blocking agents, local anesthetic agents, analgesic agents and neuroprotective agents. The μ-conopeptides are also useful for treating neuromuscular disorders. The invention is further directed to nucleic acid sequences encoding the μ-conopeptides and encoding propeptides, as well as the propeptides.

[0029] The present invention, in another aspect, relates to a pharmaceutical composition comprising an effective amount of an μ-conopeptides, a mutein thereof, an analog thereof, an active fragment thereof or pharmaceutically acceptable salts or solvates. Such a pharmaceutical composition has the capability of acting at voltage gated ion channels, and are thus useful for treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to the partial or complete blockade of voltage gated ion channels of the central nervous system comprising the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a pharmaceutical composition of the present invention.

[0030] The present invention is directed to the use of μ-conopeptides as neuromuscular blockers and for treating neuromuscular disorders. As such, the μ-conopeptides are useful for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use. Thus, in one aspect, the μ-conopeptides are useful as neurmuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration e.g., intramuscular or intravenous administration in solution. In a second aspect, the μ-conopeptides are useful as agents for treating neuromuscular disorders such as myofacial pain syndrome, chronic muscle spasm, dystonias and spasticity.

[0031] The primary factor detrimental to neurons in neurological disorders associated with deficient oxygen supply or mitochondrial dysfunction is insufficient ATP production relative to their requirement. As a large part of the energy consumed by brain cells is used for maintenance of the Na^+ gradient across the cellular membrane, reduction of energy demand by down-modulation of voltage-gated Na(+)-channels is one strategy for neuroprotection. In addition, preservation of the inward Na^+ gradient may be beneficial because it is an essential driving force for vital ion exchanges and transport mechanisms such as Ca^{2+} homeostasis and neurotransmitter uptake. Thus, the μ-conopeptides of the present invention are useful as neuroprotectants.

[0032] Thus, the pharmaceutical compositions of the present invention are useful as neuroprotectants, especially cerebroprotectants, neuromuscular blockers, analgesics (both as a

local anesthetic and for general analgesia use) or adjuvants to general anesthetics. A "neurological disorder or disease" is a disorder or disease of the nervous system including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage as in cardiac arrest or neonatal distress or epilepsy. In addition, a "neurological disorder or disease" is a disease state and condition in which a neuroprotectant, anticonvulsant, analgesic and/or as an adjunct in general anesthesia may be indicated, useful, recommended or prescribed.

[0033] More specifically, the present invention is directed to the use of these compounds for reducing neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal cord trauma, myocardial infarct, physical trauma, drowning, suffocation, perinatal asphyxia, or hypoglycemic events. The present invention is further directed to the use of these compounds for treating pain, including acute and chronic pain, such migraine, nociceptive and neuropathic pain.

[0034] A "neuroprotectant" is a compound capable of preventing the neuronal death associated with a neurological disorder or disease. An "analgesic" is a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness. A "muscle relaxant" is a compound that reduces muscular tension. An "adjunct in general anesthesia" is a compound useful in conjunction with anesthetic agents in producing the loss of ability to perceive pain associated with the loss of consciousness.

[0035] The invention relates as well to methods useful for treatment of neurological disorders and diseases, including, but not limited to, global and focal ischemic and hemorrhagic stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy or other convulsive disorders without undesirable side effects.

[0036] Thus, in one embodiment, the invention provides a method of reducing/alleviating/ decreasing the perception of pain by a subject or for inducing analgesia in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. The pain may be acute, persistent, inflammatory or neuropathic pain. The μ-conopeptides are useful as an analgesia for chronic and neuropathic pain states, such as trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, neuroma pain, phantom limb pain. These peptides are also useful for treating burn pain and as ocular anesthetics.

[0037] In a second embodiment, the invention provides a method of reducing/alleviating/ decreasing the perception of pain by a subject or for inducing analgesia, particularly local analgesia, in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof. These peptides are also useful for treating burn pain and as ocular anesthetics.

[0038] In a third embodiment, the invention provides a method of treating stroke, head or spinal cord trauma or injury, anoxia, hypoxia-induced nerve cell damage, ischemia, migraine, psychosis, anxiety, schizophrenia, inflammation, movement disorder, epilepsy, any other convulsive disorder or in the prevention of the degenerative changes connected with the same in a subject comprising administering to the subject an effective amount of the pharmaceutical composition comprising a therapeutically effective amount of a μ-conopeptide described herein or a pharmaceutically acceptable salt or solvate thereof.

[0039] In a fourth embodiment, the invention provides a method for providing a neuromuscular block or for treating neuromuscular disorders, such as methods for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use. Thus, in one aspect, the μ-conopeptides are useful as neurmuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration e.g., intramuscular or intravenous administration in solution. In a second aspect, the μ-conopeptides are useful as agents for treating neuromuscular disorders such as myofacial pain syndrome, chronic muscle spasm, dystonias and spasticity.

[0040] The present invention is also directed to the use of μ-conopeptides for screening small molecule libraries to identify small molecules that are selective blocking agents at specific sodium channel subtypes expressed in mammalian systems. In one embodiment, the blocking activity of a small molecule at a particular sodium channel subtype is compared to the blocking activity of a μ-conopeptide at the same sodium channel subtype. In a second embodiment, the ability of a small molecule to displace a μ-conopeptide from a sodium channel subtype is determined. In a third emdiment, the binding affinity of a small molecule for a sodium channel subtype is compared to the binding affinity of a μ-conopeptide for the same sodium channel subtype.

[0041] The μ-conopeptides described herein are sufficiently small to be chemically synthesized. General chemical syntheses for preparing the foregoing ω-conotoxin peptides are

described hereinafter. Various ones of the μ-conopeptides can also be obtained by isolation and purification from specific *Conus* species using the technique described in U.S. Patent Nos. 4,447,356 (Olivera et al., 1984); 5,514,774; 5,719,264; and 5,591,821, as well as in PCT published application WO 98/03189, the disclosures of which are incorporated herein by reference.

[0042] Although the μ-conopeptides of the present invention can be obtained by purification from cone snails, because the amounts of μ-conopeptides obtainable from individual snails are very small, the desired substantially pure μ-conopeptides are best practically obtained in commercially valuable amounts by chemical synthesis using solid-phase strategy. For example, the yield from a single cone snail may be about 10 micrograms or less of μ-conopeptides peptide. By "substantially pure" is meant that the peptide is present in the substantial absence of other biological molecules of the same type; it is preferably present in an amount of at least about 85% purity and preferably at least about 95% purity. Chemical synthesis of biologically active μ-conopeptides peptides depends of course upon correct determination of the amino acid sequence.

[0043] The μ-conopeptides can also be produced by recombinant DNA techniques well known in the art. Such techniques are described by Sambrook et al. (1989). A gene of interest (i.e., a gene that encodes a suitable μ-conopeptides) can be inserted into a cloning site of a suitable expression vector by using standard techniques. These techniques are well known to those skilled in the art. The expression vector containing the gene of interest may then be used to transfect the desired cell line. Standard transfection techniques such as calcium phosphate co-precipitation, DEAE-dextran transfection or electroporation may be utilized. A wide variety of host/expression vector combinations may be used to express a gene encoding a conotoxin peptide of interest. Such combinations are well known to a skilled artisan. The peptides produced in this manner are isolated, reduced if necessary, and oxidized to form the correct disulfide bonds.

[0044] One method of forming disulfide bonds in the μ-conopeptides of the present invention is the air oxidation of the linear peptides for prolonged periods under cold room temperatures or at room temperature. This procedure results in the creation of a substantial amount of the bioactive, disulfide-linked peptides. The oxidized peptides are fractionated using reverse-phase high performance liquid chromatography (HPLC) or the like, to separate peptides having different linked configurations. Thereafter, either by comparing these fractions with the elution

of the native material or by using a simple assay, the particular fraction having the correct linkage for maximum biological potency is easily determined. However, because of the dilution resulting from the presence of other fractions of less biopotency, a somewhat higher dosage may be required.

[0045] The peptides are synthesized by a suitable method, such as by exclusively solid-phase techniques, by partial solid-phase techniques, by fragment condensation or by classical solution couplings.

[0046] In conventional solution phase peptide synthesis, the peptide chain can be prepared by a series of coupling reactions in which constituent amino acids are added to the growing peptide chain in the desired sequence. Use of various coupling reagents, e.g., dicyclohexylcarbodiimide or diisopropylcarbonyldimidazole, various active esters, e.g., esters of N-hydroxyphthalimide or N-hydroxy-succinimide, and the various cleavage reagents, to carry out reaction in solution, with subsequent isolation and purification of intermediates, is well known classical peptide methodology. Classical solution synthesis is described in detail in the treatise, "Methoden der Organischen Chemie (Houben-Weyl): Synthese von Peptiden," (1974). Techniques of exclusively solid-phase synthesis are set forth in the textbook, "Solid-Phase Peptide Synthesis," (Stewart and Young, 1969), and are exemplified by the disclosure of U.S. Patent 4,105,603 (Vale et al., 1978). The fragment condensation method of synthesis is exemplified in U.S. Patent 3,972,859 (1976). Other available syntheses are exemplified by U.S. Patents No. 3,842,067 (1974) and 3,862,925 (1975). The synthesis of peptides containing γ-carboxyglutamic acid residues is exemplified by Rivier et al. (1987), Nishiuchi et al. (1993) and Zhou et al. (1996).

[0047] Common to such chemical syntheses is the protection of the labile side chain groups of the various amino acid moieties with suitable protecting groups which will prevent a chemical reaction from occurring at that site until the group is ultimately removed. Usually also common is the protection of an α-amino group on an amino acid or a fragment while that entity reacts at the carboxyl group, followed by the selective removal of the α-amino protecting group to allow subsequent reaction to take place at that location. Accordingly, it is common that, as a step in such a synthesis, an intermediate compound is produced which includes each of the amino acid residues located in its desired sequence in the peptide chain with appropriate side-chain protecting groups linked to various ones of the residues having labile side chains.

[0048] As far as the selection of a side chain amino protecting group is concerned, generally one is chosen which is not removed during deprotection of the α-amino groups during the

synthesis. However, for some amino acids, e.g., His, protection is not generally necessary. In selecting a particular side chain protecting group to be used in the synthesis of the peptides, the following general rules are followed: (a) the protecting group preferably retains its protecting properties and is not split off under coupling conditions, (b) the protecting group should be stable under the reaction conditions selected for removing the α-amino protecting group at each step of the synthesis, and (c) the side chain protecting group must be removable, upon the completion of the synthesis containing the desired amino acid sequence, under reaction conditions that will not undesirably alter the peptide chain.

[0049] It should be possible to prepare many, or even all, of these peptides using recombinant DNA technology. However, when peptides are not so prepared, they are preferably prepared using the Merrifield solid-phase synthesis, although other equivalent chemical syntheses known in the art can also be used as previously mentioned. Solid-phase synthesis is commenced from the C-terminus of the peptide by coupling a protected α-amino acid to a suitable resin. Such a starting material can be prepared by attaching an α-amino-protected amino acid by an ester linkage to a chloromethylated resin or a hydroxymethyl resin, or by an amide bond to a benzhydrylamine (BHA) resin or paramethylbenzhydrylamine (MBHA) resin. Preparation of the hydroxymethyl resin is described by Bodansky et al. (1966). Chloromethylated resins are commercially available from Bio Rad Laboratories (Richmond, CA) and from Lab. Systems, Inc. The preparation of such a resin is described by Stewart and Young (1969). BHA and MBHA resin supports are commercially available, and are generally used when the desired polypeptide being synthesized has an unsubstituted amide at the C-terminus. Thus, solid resin supports may be any of those known in the art, such as one having the formulae -O-CH_2-resin support, -NH BHA resin support, or -NH-MBHA resin support. When the unsubstituted amide is desired, use of a BHA or MBHA resin is preferred, because cleavage directly gives the amide. In case the N-methyl amide is desired, it can be generated from an N-methyl BHA resin. Should other substituted amides be desired, the teaching of U.S. Patent No. 4,569,967 (Kornreich et al., 1986) can be used, or should still other groups than the free acid be desired at the C-terminus, it may be preferable to synthesize the peptide using classical methods as set forth in the Houben-Weyl text (1974).

[0050] The C-terminal amino acid, protected by Boc or Fmoc and by a side-chain protecting group, if appropriate, can be first coupled to a chloromethylated resin according to the procedure set forth in K. Horiki et al. (1978), using KF in DMF at about 60°C for 24 hours with stirring,

when a peptide having free acid at the C-terminus is to be synthesized. Following the coupling of the BOC-protected amino acid to the resin support, the α-amino protecting group is removed, as by using trifluoroacetic acid (TFA) in methylene chloride or TFA alone. The deprotection is carried out at a temperature between about 0°C and room temperature. Other standard cleaving reagents, such as HCl in dioxane, and conditions for removal of specific α-amino protecting groups may be used as described in Schroder & Lubke (1965).

[0051] After removal of the α-amino-protecting group, the remaining α-amino- and side chain-protected amino acids are coupled step-wise in the desired order to obtain the intermediate compound defined hereinbefore, or as an alternative to adding each amino acid separately in the synthesis, some of them may be coupled to one another prior to addition to the solid phase reactor. Selection of an appropriate coupling reagent is within the skill of the art. Particularly suitable as a coupling reagent is N,N'-dicyclohexylcarbodiimide (DCC, DIC, HBTU, HATU, TBTU in the presence of HoBt or HoAt).

[0052] The activating reagents used in the solid phase synthesis of the peptides are well known in the peptide art. Examples of suitable activating reagents are carbodiimides, such as N,N'-diisopropylcarbodiimide and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide. Other activating reagents and their use in peptide coupling are described by Schroder & Lubke (1965) and Kapoor (1970).

[0053] Each protected amino acid or amino acid sequence is introduced into the solid-phase reactor in about a twofold or more excess, and the coupling may be carried out in a medium of dimethylformamide (DMF):CH_2Cl_2 (1:1) or in DMF or CH_2Cl_2 alone. In cases where intermediate coupling occurs, the coupling procedure is repeated before removal of the α-amino protecting group prior to the coupling of the next amino acid. The success of the coupling reaction at each stage of the synthesis, if performed manually, is preferably monitored by the ninhydrin reaction, as described by Kaiser et al. (1970). Coupling reactions can be performed automatically, as on a Beckman 990 automatic synthesizer, using a program such as that reported in Rivier et al. (1978).

[0054] After the desired amino acid sequence has been completed, the intermediate peptide can be removed from the resin support by treatment with a reagent, such as liquid hydrogen fluoride or TFA (if using Fmoc chemistry), which not only cleaves the peptide from the resin but also cleaves all remaining side chain protecting groups and also the -amino protecting group at the N-terminus if it was not previously removed to obtain the peptide in the form of the free

acid. If Met is present in the sequence, the Boc protecting group is preferably first removed using trifluoroacetic acid (TFA)/ethanedithiol prior to cleaving the peptide from the resin with HF to eliminate potential S-alkylation. When using hydrogen fluoride or TFA for cleaving, one or more scavengers such as anisole, cresol, dimethyl sulfide and methylethyl sulfide are included in the reaction vessel.

[0055] Cyclization of the linear peptide is preferably affected, as opposed to cyclizing the peptide while a part of the peptido-resin, to create bonds between Cys residues. To effect such a disulfide cyclizing linkage, fully protected peptide can be cleaved from a hydroxymethylated resin or a chloromethylated resin support by ammonolysis, as is well known in the art, to yield the fully protected amide intermediate, which is thereafter suitably cyclized and deprotected. Alternatively, deprotection, as well as cleavage of the peptide from the above resins or a benzhydrylamine (BHA) resin or a methylbenzhydrylamine (MBHA), can take place at 0°C with hydrofluoric acid (HF) or TFA, followed by oxidation as described above.

[0056] The peptides are also synthesized using an automatic synthesizer. Amino acids are sequentially coupled to an MBHA Rink resin (typically 100 mg of resin) beginning at the C-terminus using an Advanced Chemtech 357 Automatic Peptide Synthesizer. Couplings are carried out using 1,3-diisopropylcarbodimide in N-methylpyrrolidinone (NMP) or by 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and diethylisopropylethylamine (DIEA). The FMOC protecting group is removed by treatment with a 20% solution of piperidine in dimethylformamide(DMF). Resins are subsequently washed with DMF (twice), followed by methanol and NMP.

[0057] Muteins, analogs or active fragments, of the foregoing conotoxin peptides are also contemplated here. See, e.g., Hammerland et al. (1992). Derivative muteins, analogs or active fragments of the conotoxin peptides may be synthesized according to known techniques, including conservative amino acid substitutions, such as outlined in U.S. Patent Nos. 5,545,723 (see particularly col. 2, line 50--col. 3, line 8); 5,534,615 (see particularly col. 19, line 45--col. 22, line 33); and 5,364,769 (see particularly col. 4, line 55--col. 7, line 26), each herein incorporated by reference.

[0058] The μ-conopeptides of the present invention are also useful to reduce neurotoxic injury associated with conditions of hypoxia, anoxia or ischemia which typically follows stroke, cerebrovascular accident, brain or spinal chord trauma, myocardial infarct, physical trauma, drownings, suffocation, perinatal asphyxia, or hypoglycemic events. To reduce neurotoxic

injury, an ω-conopeptide should be administered in a therapeutically effective amount to the patient within 24 hours of the onset of the hypoxic, anoxic or ischemic condition in order for the μ-conopeptide to effectively minimize the CNS damage which the patient will experience.

[0059] The μ-conopeptides of the present invention are further useful in controlling pain, e.g., as analgesic agents, and the treatment of migraine, acute pain or persistent pain. They can be used prophylactically or to relieve the symptoms associated with a migraine episode, or to treat acute or persistent pain. For these uses, an μ-conopeptide is administered in a therapeutically effective amount to overcome or to ease the pain.

[0060] The μ-conopeptides of the present invention are also useful as neuromuscular blockers and for treating neuromuscular disorders. They can be used for providing relaxation of muscle, for treating benign essential blepharospasm and other forms of focal dystonia and for anti-wrinkle use. Thus, in one aspect, the μ-conopeptides are used as neurmuscular blocking agents in conjunction with surgery or for intubation of the trachea by conventional parenteral administration e.g., intramuscular or intravenous administration in solution. In a second aspect, the μ-conopeptides are used as agents for treating neuromuscular disorders such as myofacial pain syndrome, chronic muscle spasm, dystonias and spasticity. For these uses, a μ-conopeptide is administered in a therapeutically effective amount to relax muscle or provide a neuromuscular block.

[0061] Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques. See, for example, *Remington's Pharmaceutical Sciences*, 18th Ed. (1990, Mack Publishing Co., Easton, PA). Typically, an antagonistic amount of active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral, parenteral or intrathecally. For examples of delivery methods see U.S. Patent No. 5,844,077, incorporated herein by reference.

[0062] "Pharmaceutical composition" means physically discrete coherent portions suitable for medical administration. "Pharmaceutical composition in dosage unit form" means physically discrete coherent units suitable for medical administration, each containing a daily dose or a multiple (up to four times) or a sub-multiple (down to a fortieth) of a daily dose of the active compound in association with a carrier and/or enclosed within an envelope. Whether the composition contains a daily dose, or for example, a half, a third or a quarter of a daily dose, will

depend on whether the pharmaceutical composition is to be administered once or, for example, twice, three times or four times a day, respectively.

[0063] The term "salt", as used herein, denotes acidic and/or basic salts, formed with inorganic or organic acids and/or bases, preferably basic salts. While pharmaceutically acceptable salts are preferred, particularly when employing the compounds of the invention as medicaments, other salts find utility, for example, in processing these compounds, or where non-medicament-type uses are contemplated. Salts of these compounds may be prepared by art-recognized techniques.

[0064] Examples of such pharmaceutically acceptable salts include, but are not limited to, inorganic and organic addition salts, such as hydrochloride, sulphates, nitrates or phosphates and acetates, trifluoroacetates, propionates, succinates, benzoates, citrates, tartrates, fumarates, maleates, methane-sulfonates, isothionates, theophylline acetates, salicylates, respectively, or the like. Lower alkyl quaternary ammonium salts and the like are suitable, as well.

[0065] As used herein, the term "pharmaceutically acceptable" carrier means a non-toxic, inert solid, semi-solid liquid filler, diluent, encapsulating material, formulation auxiliary of any type, or simply a sterile aqueous medium, such as saline. Some examples of the materials that can serve as pharmaceutically acceptable carriers are sugars, such as lactose, glucose and sucrose, starches such as corn starch and potato starch, cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt, gelatin, talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol, polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline, Ringer's solution; ethyl alcohol and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations.

[0066] Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. Examples of pharmaceutically acceptable antioxidants include, but are not limited to, water soluble antioxidants such as ascorbic acid, cysteine hydrochloride, sodium bisulfite, sodium metabisulfite, sodium sulfite,

and the like; oil soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, aloha-tocopherol and the like; and the metal chelating agents such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

[0067] For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698.

[0068] For parenteral administration, the compound may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they may also be dissolved in cerebrospinal fluid.

[0069] A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, epidural, irrigation, intramuscular, release pumps, or infusion.

[0070] For example, administration of the active agent according to this invention may be achieved using any suitable delivery means, including:

(a) pump (see, e.g., Luer & Hatton (1993), Zimm et al. (1984) and Ettinger et al. (1978));

(b), microencapsulation (see, e.g., U.S. Patent Nos. 4,352,883; 4,353,888; and 5,084,350);

(c) continuous release polymer implants (see, e.g., U.S. Patent No. 4,883,666);

(d) macroencapsulation (see, e.g., U.S. Patent Nos. 5,284,761, 5,158,881, 4,976,859 and 4,968,733 and published PCT patent applications WO92/19195, WO 95/05452);

(e) naked or unencapsulated cell grafts to the CNS (see, e.g., U.S. Patent Nos. 5,082,670 and 5,618,531);

(f) injection, either subcutaneously, intravenously, intra-arterially, intramuscularly, or to other suitable site; or

(g) oral administration, in capsule, liquid, tablet, pill, or prolonged release formulation.

[0071] In one embodiment of this invention, an active agent is delivered directly into the CNS, preferably to the brain ventricles, brain parenchyma, the intrathecal space or other suitable CNS location, most preferably intrathecally.

[0072] Alternatively, targeting therapies may be used to deliver the active agent more specifically to certain types of cell, by the use of targeting systems such as antibodies or cell specific ligands. Targeting may be desirable for a variety of reasons, e.g. if the agent is unacceptably toxic, or if it would otherwise require too high a dosage, or if it would not otherwise be able to enter the target cells.

[0073] The active agents, which are peptides, can also be administered in a cell based delivery system in which a DNA sequence encoding an active agent is introduced into cells designed for implantation in the body of the patient, especially in the spinal cord region. Suitable delivery systems are described in U.S. Patent No. 5,550,050 and published PCT Application Nos. WO 92/19195, WO 94/25503, WO 95/01203, WO 95/05452, WO 96/02286, WO 96/02646, WO 96/40871, WO 96/40959 and WO 97/12635. Suitable DNA sequences can be prepared synthetically for each active agent on the basis of the developed sequences and the known genetic code.

[0074] Exemplary methods for administering such muscle relaxant compounds (e.g., so as to achieve sterile or aseptic conditions) will be apparent to the skilled artisan. Certain methods suitable for administering compounds useful according to the present invention are set forth in

Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 7th Ed. (1985). The administration to the patient can be intermittent; or at a gradual, continuous, constant or controlled rate. Administration can be to a warm-blooded animal (e.g. a mammal, such as a mouse, rat, cat, rabbit, dog, pig, cow or monkey); but advantageously is administered to a human being. Administration occurs after general anesthesia is administered. The frequency of administration normally is determined by an anesthesiologist, and typically varies from patient to patient.

[0075] The active agent is preferably administered in an therapeutically effective amount. By a "therapeutically effective amount" or simply "effective amount" of an active compound is meant a sufficient amount of the compound to treat the desired condition at a reasonable benefit/risk ratio applicable to any medical treatment. The actual amount administered, and the rate and time-course of administration, will depend on the nature and severity of the condition being treated. Prescription of treatment, e.g. decisions on dosage, timing, etc., is within the responsibility of general practitioners or spealists, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of techniques and protocols can be found in *Remington's Parmaceutical Sciences*.

[0076] Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Typically the active agents of the present invention exhibit their effect at a dosage range from about 0.001 mg/kg to about 250 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg of the active ingredient, more preferably from a bout 0.05 mg/kg to about 75 mg/kg. A suitable dose can be administered in multiple sub-doses per day. Typically, a dose or sub-dose may contain from about 0.1 mg to about 500 mg of the active ingredient per unit dosage form. A more preferred dosage will contain from about 0.5 mg to about 100 mg of active ingredient per unit dosage form. Dosages are generally initiated at lower levels and increased until desired effects are achieved. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

[0077] For the treatment of pain, if the route of administration is directly to the CNS, the dosage contemplated is from about 1 ng to about 100 mg per day, preferably from about 100 ng

to about 10 mg per day, more preferably from about 1 μg to about 100 μg per day. If administered peripherally, the dosage contemplated is somewhat higher, from about 100 ng to about 1000 mg per day, preferably from about 10 μg to about 100 mg per day, more preferably from about 100 μg to about 10 mg per day. If the conopeptide is delivered by continuous infusion (e.g., by pump delivery, biodegradable polymer delivery or cell-based delivery), then a lower dosage is contemplated than for bolus delivery.

[0078] Advantageously, the compositions are formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredients. Tablets, coated tablets, capsules, ampoules and suppositories are examples of dosage forms according to the invention.

[0079] It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be consistent with the dosage form employed in single or multiple unit doses. The exact individual dosages, as well as daily dosages, are determined according to standard medical principles under the direction of a physician or veterinarian for use humans or animals.

[0080] The pharmaceutical compositions will generally contain from about 0.0001 to 99 wt. %, preferably about 0.001 to 50 wt. %, more preferably about 0.01 to 10 wt.% of the active ingredient by weight of the total composition. In addition to the active agent, the pharmaceutical compositions and medicaments can also contain other pharmaceutically active compounds. Examples of other pharmaceutically active compounds include, but are not limited to, analgesic agents, cytokines and therapeutic agents in all of the major areas of clinical medicine. When used with other pharmaceutically active compounds, the conopeptides of the present invention may be delivered in the form of drug cocktails. A cocktail is a mixture of any one of the compounds useful with this invention with another drug or agent. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, pump, injectable solution, etc.) would contain both the instant composition in combination supplementary potentiating agent. The individual drugs of the cocktail are each administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters described above; but, in any event, is that amount which establishes a level of the drugs in the area of body where the drugs are required for a period of time which is effective in attaining the desired effects.

[0081] The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA,

genetics, immunology, cell biology, cell culture and transgenic biology, which are within the skill of the art. See, e.g., Maniatis *et al.*, 1982; Sambrook *et al.*, 1989; Ausubel *et al.*, 1992; Glover, 1985; Anand, 1992; Guthrie and Fink, 1991; Harlow and Lane, 1988; Jakoby and Pastan, 1979; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); *Culture Of Animal Cells* (R. I. Freshney, Alan R. Liss, Inc., 1987); *Immobilized Cells And Enzymes* (IRL Press, 1986); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); *Methods In Enzymology*, Vols. 154 and 155 (Wu et al. eds.), *Immunochemical Methods In Cell And Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Riott, *Essential Immunology*, 6th Edition, Blackwell Scientific Publications, Oxford, 1988; Hogan et al., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

EXAMPLES

[0082] The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Isolation of μ-Conopeptides

[0083] Crude venom was extracted from venom ducts (Cruz et al., 1976), and the components were purified as previously described (Cartier et al., 1996). The crude extract from venom ducts was purified by reverse phase liquid chromatography (RPLC) using a Vydac C_{18} semi-preparative column (10 x 250 mm). Further purification of bioactive peaks was done on a Vydac C_{18} analytical column (4.6 x 220 mm). The effluents were monitored at 220 nm. Peaks were collected, and aliquots were assayed for activity. Throughout purification, HPLC fractions were assayed by means of intracerebral ventricular (i.c.v.) injection into mice (Clark et al., 1981).

[0084] The amino acid sequence of the purified peptides were determined by standard methods. The purified peptides were reduced and alkylated prior to sequencing by automated Edman degradation on an Applied Biosystems 477A Protein Sequencer with a 120A Analyzer (DNA/Peptide Facility, University of Utah) (Martinez et al., 1995; Shon et al., 1994).

[0085] In accordance with this method, the μ-conopeptides described as "isolated" in Table 1 were obtained. These μ-conopeptides, as well as the other μ-conopeptides and the μ-conopeptide precursors set forth in Table 1 are synthesized as described in U.S. Patent No. 5,670,622.

EXAMPLE 2

Isolation of DNA Encoding μ-Conopeptides

[0086] DNA coding for μ-conopeptides was isolated and cloned in accordance with conventional techniques using general procedures well known in the art, such as described in Olivera et al. (1996). Alternatively, cDNA libraries was prepared from *Conus* venom duct using conventional techniques. DNA from single clones was amplified by conventional techniques using primers which correspond approximately to the M13 universal priming site and the M13 reverse universal priming site. Clones having a size of approximately 300-500 nucleotides were sequenced and screened for similarity in sequence to known μ-conotoxins. The DNA sequences and encoded propeptide sequences are set forth in Table 1. DNA sequences coding for the mature toxin can also be prepared on the basis of the DNA sequences set forth in Table1. An alignment of the μ-conopeptides of the present invention is set forth in Table 2.

TABLE 1

DNA and Amino Acid Sequences of μ-Conopeptides and Precursors

Name: Ar3.1
Species: arenatus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTCTTGACCATCTG
TATGCTTCTGTTTCCCCTTACTGCTCTTCCGCTGGATGGGGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGACGACTTTATAACTGAGCATCATCCCCTGTTTGATCC
TGTCAAACGGTGTTGCGAGAGGCCATGCAACATAGGATGCGTACCTTGTTGTTAATG
ACCAGCTTTGTCATCGCGGCCTCATCAAGCGAATAAGTAAAACGATTGCAGT (SEQ ID NO:1)

Translation:
MMSKLGVFLTICMLLFPLTALPLDGDQPADRPAERMQDDFITEHHPLFDPVKRCCERPC
NIGCVPCC (SEQ ID NO:2)

Toxin Sequence:
Cys-Cys-Xaa1-Arg-Xaa3-Cys-Asn-Ile-Gly-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:3)

Name: Ak3.1
Species: atlanticus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCAC
TTACTGCTCTTCCGCTGGATGAAGATCAACCGGTACACCGACCTGCAGAGCGTATGC
AGGACATTTCATCTGATCAACATCTCTTCTTTGATCTCATCAAACGGTGCTGCGAGT
TGCCATGCGGGCCAGGCTTTTGCGTCCCTTGTTGCTGACATCAATAACGTGTTGATG
ACCAACTTTCTCGAG (SEQ ID NO:4)

Translation:
GSMMSKLGVLLTICLLLFPLTALPLDEDQPVHRPAERMQDISSDQHLFFDLIKRCCELPCG
PGFCVPCC (SEQ ID NO:5)

Toxin Sequence:
Cys-Cys-Xaa1-Leu-Xaa3-Cys-Gly-Xaa3-Gly-Phe-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:6)

Name: A3.1
Species: aurisiacus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TTTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAATCTGTAGACCGA
CCTGAAGAGCGTATGCAGGACGACATTTCATCTGAGCAGCATCCCTTGTTTAATCAG
AAAAGAATGTGTTGCGGCGAAGGCCGGAAATGCCCCAGCTATTTCAGAAACAGTCA
GATTTGTCATTGTTGTTAAATGACAACGTGTCGATGACCAACTTCGTTATCACGACT
AATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:7)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQSVDRPEERMQDDISSEQHPLFNQKRMCCGEGR
KCPSYFRNSQICHCC (SEQ ID NO:8)

Toxin Sequence:
Met-Cys-Cys-Gly-Xaa1-Gly-Arg-Lys-Cys-Xaa3-Ser-Xaa5-Phe-Arg-Asn-Ser-Gln-Ile-Cys-His-Cys-Cys-^ (SEQ ID NO:9)

Name: A3.2
Species: aurisiacus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTTTGCTTCTGTTTCCCC
TTACTGCTCTTCCGATCGATGGAGATCAATCTGTAGACCGACCTGCAGAGCGTATGC
AGGATGACATTTCATCTGAGCAGCATCGCTTGTTCAATCAGAAAAGAAGGTGCTGC
CGGTGGCCATGCCCCCGACAAATCGACGGTGAATATTGTGGCTGTTGCCTTGGATGA
TAACCGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:10)

Translation:
GSMMSKLGVLLTICLLLFPLTALPIDGDQSVDRPAERMQDDISSEQHRLFNQKRRCCRW
PCPRQIDGEYCGCCLG (SEQ ID NO:11)

Toxin Sequence:
Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Arg-Gln-Ile-Asp-Gly-Xaa1-Xaa5-Cys-Gly-Cys-Cys-Leu-#
(SEQ ID NO:12)

Name: A3.3
Species: aurisiacus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTACTTCTGTTTCCCC
TTACTGCTTTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCAGATCGTATGC
AGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAAGAGACAAAAGTGTTGCA
CTGGGAAGAAGGGGTCATGCTCCGGCAAAGCATGCAAAAATCTCAAATGTTGCTCT
GGACGATAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:13)

Translation:
GSMMSKLGVLLTICLLLFPLTAFPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCTG
KKGSCSGKACKNLKCCSGR (SEQ ID NO:14)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-Cys-
Cys-Ser-# (SEQ ID NO:15)

Name: A3.4
Species: aurisiacus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGCTGACCATCTGTCTGCTTCTGTTTCCAC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTCTAGACCGACACGCGGAGCGTATGC
ATGATGGCATTTCACCTAAACGCCATCCCTGGTTTGATCCCGTCAAACGGTGTTGCA

AGGTGCAATGCGAGTCTTGCACCCCTTGTTGCTAACGTGTTGATGACCAACTTTCTC
GAG (SEQ ID NO:16)

Translation:
GSMMSKLGVLLTICLLLFPLTAVPLDGDQPLDRHAERMHDGISPKRHPWFDPVKRCCKV
QCESCTPCC (SEQ ID NO:17)

Toxin Sequence:
Cys-Cys-Lys-Val-Gln-Cys-Xaa1-Ser-Cys-Thr-Xaa3-Cys-Cys-^ (SEQ ID NO:18)

Name: Bn3.1
Species: bandanus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTATGCTTCTGTTTCCCC
TCACTGCTCTTCCGATGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTAGT
CAGGACGTTTCATCTGAACAGCATCCCTTGTTTGATCCCGTCAAACGGTGTTGCAAC
TGGCCATGCTCCATGGGATGCATCCCTTGTTGCTACTATTAATAACGTGTTGATGAC
CAACTTTCTCGAG (SEQ ID NO:19)

Translation:
GSMMSKLGVLLTICMLLFPLTALPMDGDQPADRPAERSQDVSSEQHPLFDPVKRCCNW
PCSMGCIPCCYY (SEQ ID NO:20)

Toxin Sequence:
Cys-Cys-Asn-Xaa4-Xaa3-Cys-Ser-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Xaa5-Xaa5-^ (SEQ ID
NO:21)

Name: Bt3.1
Species: betulinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCTTCTG
TCTGCTTCTGTTTCCCCTGACTGCTCTTCCGCTGGATGAAGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGACATTTCATCTGAACAGCATCCCTTGTTTGATCCCGT
CAAACGGTGTTGCGAATTGCCATGCCATGGATGCGTCCCTTGTTGCTGGCCTTAATA
ACGTGTGGATGACCAACTGTGTTATCACGGCCACGTCAAGTGTCTAATGAATAAGT
AAAATGATTGCAGT (SEQ ID NO:22)

Translation:
MMSKLGVLLTFCLLLFPLTALPLDEDQPADRPAERMQDISSEQHPLFDPVKRCCELPCHG
CVPCCWP (SEQ ID NO:23)

Toxin Sequence:

Cys-Cys-Xaa1-Leu-Xaa3-Cys-His-Gly-Cys-Val-Xaa3-Cys-Cys-Xaa4-Xaa3-^ (SEQ ID NO:24)

Name: Bt3.2
Species: betulinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCTTCTG
TCTGCTTCTGTTTCCCCTGACTGCTCTTCCGCTGGATGAAGATCAACCTGCAGACCG
ACATGCAGAGCGTATGCAGGACATTTCACCTGAACAGCATCCCTCGTTTGATCCCGT
CAAACGGTGTTGCGGGCTGCCATGCAATGGATGCGTCCCTTGTTGCTGGCCTTCATA
ACGTGTGGACGACCAACTTTGTTATCACGGCCACGTCAAGTGTCTGATGAATAAGTA
AAACGATTGCAGT (SEQ ID NO:25)

Translation:
MMSKLGVLLTFCLLLFPLTALPLDEDQPADRHAERMQDISPEQHPSFDPVKRCCGLPCN
GCVPCCWPS (SEQ ID NO:26)

Toxin Sequence:
Cys-Cys-Gly-Leu-Xaa3-Cys-Asn-Gly-Cys-Val-Xaa3-Cys-Cys-Xaa4-Xaa3-Ser-^ (SEQ ID NO:27)

Name: Bt3.3
Species: betulinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTTTAAACTGGGAGTCTTGTTGACCATCTA
TATGCTTCTGTTTCCCTTTACTGCTCTTCCGCTGGATGGAGATCAACCTGCAGACCAA
CCTCTAGAGCGCATGCAGTATGACATGTTACGTGCAGTGAATCCCTGGTTTGATCCC
GTCAAAAGGTGCTGCTCGAGGAACTGCGCAGTATGCATCCCTTGTTGCCCGAATTGG
CCAGCTTGATTATCGCGGCCAAGAGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:28)

Translation:
MMFKLGVLLTIYMLLFPFTALPLDGDQPADQPLERMQYDMLRAVNPWFDPVKRCCSR
NCAVCIPCCPNWPA (SEQ ID NO:29)

Toxin Sequence:
Cys-Cys-Ser-Arg-Asn-Cys-Ala-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Asn-Xaa4-Xaa3-Ala-^ (SEQ ID NO:30)

Name: Bu3.1
Species: bullatus

Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTTTTGCTCTTCCGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCAGAATTCCTTGCTTGAGAA
GAGAGTTACTGACAGGTGCTGCAAAGGGAAGAGGGAATGCGGCAGATGGTGCAGA
GATCACTCGCGTTGTTGCGGTCGACGATAAGCTGTTGATGACCAGCTTTGTTATCAC
GGCTACATCAAGTGTCTAGTGAATAAGTAAAATGATTGCAGT (SEQ ID NO:31)

Translation:
MMSKLGVLLTICLLLFPLFALPQDGDQPADRPAERMQDDISSEQNSLLEKRVTDRCCKG
KRECGRWCRDHSRCCGRR (SEQ ID NO:32)

Toxin Sequence:
Val-Thr-Asp-Arg-Cys-Cys-Lys-Gly-Lys-Arg-Xaa1-Cys-Gly-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:33)

Name: Bu3.1A
Species: bullatus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTTTTGCTCTTCGGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAGGATGACATTTCATCTGAGCAGAATCCCTTGCTTGAGAA
GAGAGTTGGTGACAGGTGCTGCAAAGGGAAGAGGGGGTGCGGCAGATGGTGCAGA
GATCACTCACGTTGTTGCGGTCGACGATAACGTGTTGATGACCAGCTTTGTTATCAC
GGCTACATCAAGTGTCTTAGTGATTAAGTAAAACGATTGCAGT (SEQ ID NO:34)

Translation:
MMSKLGVLLTICLLLFPLFALRQDGDQPADRPAERMQDDISSEQNPLLEKRVGDRCCKG
KRGCGRWCRDHSRCCGRR (SEQ ID NO:35)

Toxin Sequence:
Val-Gly-Asp-Arg-Cys-Cys-Lys-Gly-Lys-Arg-Gly-Cys-Gly-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:36)

Name: Bu3.2
Species: bullatus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTTTTGCTCTTCCGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCAGAATCCCTTGCTTGAGAA

GAGAGTTGGTGAAAGGTGCTGCAAAAACGGGAAGAGGGGGTGCGGCAGATGGTGC
AGAGATCACTCACGTTGTTGCGGTCGACGATAACGTGTTGATGACCGAGGCTTTCGT
TATCACGGCTACATCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID
NO:37)

Translation:
MMSKLGVLLTICLLLFPLFALPQDGDQPADRPAERMQDDISSEQNPLLEKRVGERCCKN
GKRGCGRWCRDHSRCCGRR (SEQ ID NO:38)

Toxin Sequence:
Val-Gly-Xaa1-Arg-Cys-Cys-Lys-Asn-Gly-Lys-Arg-Gly-Cys-Gly-Arg-Xaa4-Cys-Arg-Asp-His-
Ser-Arg-Cys-Cys-# (SEQ ID NO:39)

Name: Bu3.3
Species: bullatus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTTTTGCTCTTCCGCAGGACGGAGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGACGACCTTTCATCTGAGCAGCATCCCTTGTTTGAGAA
GAGAATTGTTGACAGGTGCTGCAACAAAGGGAACGGGAAGAGGGGGTGCAGCAGA
TGGTGCAGAGATCACTCACGTTGTTGCGGTCGACGATGAACTGTTGATGACCGAGG
CTTTGGTTATCACGGCTACATCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT
(SEQ ID NO:40)

Translation:
MMSKLGVLLTICLLLFPLFALPQDGDQPADRPAERMQDDLSSEQHPLFEKRIVDRCCNK
GNGKRGCSRWCRDHSRCCGRR (SEQ ID NO:41)

Toxin Sequence:
Ile-Val-Asp-Arg-Cys-Cys-Asn-Lys-Gly-Asn-Gly-Lys-Arg-Gly-Cys-Ser-Arg-Xaa4-Cys-Arg-
Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:42)

Name: Bu3.4
Species: bullatus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTTTTGCTCTTCCGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCTGAGCGTATGCAGGACGACATTTCATCTGAGCGGAATCCCTTGTTTGAGAAG
AGCGTTGGTTTATATTGCTGCCGACCCAAACCCAACGGGCAGATGATGTGCGACAG
ATGGTGCGAAAAAAACTCACGTTGTTGCGGTCGACGATAATGTGTTGATGACCAGC
TTTGTTATCAAGGCTACATCAAGTATCTAGTGAATAAGTAAAACGATTGCAGT (SEQ
ID NO:43)

Translation:
MMSKLGVLLTICLLLFPLFALPQDGDQPADRPAERMQDDISSERNPLFEKSVGLYCCRPK
PNGQMMCDRWCEKNSRCCGRR (SEQ ID NO:44)

Toxin Sequence:
Val-Gly-Leu-Xaa5-Cys-Cys-Arg-Xaa3-Lys-Xaa3-Asn-Gly-Gln-Met-Met-Cys-Asp-Arg-Xaa4-Cys-Xaa1-Lys-Asn-Ser-Arg-Cys-Cys-# (SEQ ID NO:45)

Name: Bu3.5
Species: bullatus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTTTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAATCTGTAGACCGA
CCTGCAGAACGTATGCAGGACGACCTTTCATCTGAGCAGCATCCCTTGTTTGTTCAG
AAAAGAAGGTGTTGCGGCGAAGGCTTGACATGCCCCAGATATTGGAAAAACAGTCA
GATTTGTGCTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCGGTATCACGACT
ACGCCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:46)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQSVDRPAERMQDDLSSEQHPLFVQKRRCCGEGL
TCPRYWKNSQICACC (SEQ ID NO:47)

Toxin Sequence:
Arg-Cys-Cys-Gly-Xaa1-Gly-Leu-Thr-Cys-Xaa3-Arg-Xaa5-Xaa4-Lys-Asn-Ser-Gln-Ile-Cys-Ala-Cys-Cys-^ (SEQ ID NO:48)

Name: Bu3.5A
Species: bullatus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTTTTGCTCTTCCGCAGGATGGAGATCAACCTGCAGACCGA
CCTGCTGAGCGTATGCAGGACGACATTTCATCTGAGCAGGATCCCTTGTTTGTTCAG
AAAAGAAGGTGTTGCGGCGAAGGCTTGACATGCCCCAGATATTGGAAAAACAGTCA
GATTTGTGCTTGTTGTTAAATGACAACGTGTGATGACCAACTTCGGTATCACGACTA
CGCCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:49)

Translation:
MMSKLGVLLTICLLLFPLFALPQDGDQPADRPAERMQDDISSEQDPLFVQKRRCCGEGL
TCPRYWKNSQICACC (SEQ ID NO:50)

Toxin Sequence:
Arg-Cys-Cys-Gly-Xaa1-Gly-Leu-Thr-Cys-Xaa3-Arg-Xaa5-Xaa4-Lys-Asn-Ser-Gln-Ile-Cys-Ala-Cys-Cys-^ (SEQ ID NO:51)

Name: Cp3.1
Species: capitaneus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGGTGACCATCTGCCTGCTTCTGTTTCCC
CTTGCTGCTTTTCCACTGGATGGAAATCAACCTGCAGACCACCCTGCAAAGCGTACG
CAAGATGACAGTTCAGCTGCCCTGATCAATACCTGGATTGATCATTCCCATTCTTGC
TGCAGGGACTGCGGTGAAGATTGTGTTGGTTGTTGCCGGTAACGTGTTGATGACCAA
CTTTCTCGAG (SEQ ID NO:52)

Translation:
GSMMSKLGVLVTICLLLFPLAAFPLDGNQPADHPAKRTQDDSSAALINTWIDHSHSCCR
DCGEDCVGCCR (SEQ ID NO:53)

Toxin Sequence:
Ser-Cys-Cys-Arg-Asp-Cys-Gly-Xaa1-Asp-Cys-Val-Gly-Cys-Cys-Arg-^ (SEQ ID NO:54)

Name: Ca3.1
Species: caracteristicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCAATGGATGGAGATCAACCTGCAGACCA
ACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAT
GAGAAAAAGGTGTTGCGGCCCCGGCGGTTCATGCCCCGTATATTTCAGAGACAATT
TTATTTGTGGTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCATTATCACGAC
TACGCCAAGTGTCTAATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:55)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQDDISSEQYPLFDMRKRCCGPG
GSCPVYFRDNFICGCC (SEQ ID NO:56)

Toxin Sequence:
Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Arg-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:57)

Name: Ca3.2
Species: caracteristicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATGAACCTGCAAACCG
ACCTGTCGAGCGTATGCAGGACAACATTTCATCTGAGCAGTATCCCTTGTTTGAGAA
GAGACGAGATTGTTGCACTCCGCCGAAGAAATGCAAAGACCGACAATGCAAACCCC
AGAGATGTTGCGCTGGACGATAACGTGTTGATGACCAACTTTATCACGGCTACGTCA
AGTGTTTAGTGAATAAGTAAAATGATTGCAGT (SEQ ID NO:58)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPK
KCKDRQCKPQRCCAGR (SEQ ID NO:59)

Toxin Sequence:
Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Gln-Cys-Lys-Xaa3-Gln-Arg-Cys-Cys-Ala-# (SEQ ID NO:60)

Name: Ca3.3
Species: caracteristicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCACTGGATGGAGATCAACCTGCAGATCAA
TCTGCAGAGCGACCTGCAGAGCGTACGCAGGACGACATTCAGCAGCATCCGTTATA
TGATCCGAAAAGAAGGTGTTGCCGTTATCCATGCCCCGACAGCTGCCACGGATCTTG
CTGCTATAAGTGATAACATGTTGATGGCCAGCTTTGTTATCACGGCCACGTCAAGTG
TCTTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:61)

Translation:
MMSKLGVLLTICLLLFPLTALPLDGDQPADQSAERPAERTQDDIQQHPLYDPKRRCCRY
PCPDSCHGSCCYK (SEQ ID NO:62)

Toxin Sequence:
Arg-Cys-Cys-Arg-Xaa5-Xaa3-Cys-Xaa3-Asp-Ser-Cys-His-Gly-Ser-Cys-Cys-Xaa5-Lys-^ (SEQ ID NO:63)

Name: Ca3.4
Species: caracteristicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCACAGCGTCTGCAGGACCGCATTCCAACTGAAGATCATCCCTTATTTGATC
CCAACAAACGGTGTTGCCCGCCGGTGGCATGCAACATGGGATGCAAGCCTTGTTGT

GGATGACCAGCTTTGTTATCGCGGTCTTCATGAAGTGTCTTAATGAATAAGTAAAAT
GATTGCAGT (SEQ ID NO:64)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAQRLQDRIPTEDHPLFDPNKRCCPPVA
CNMGCKPCCG (SEQ ID NO:65)

Toxin Sequence:
Cys-Cys-Xaa3-Xaa3-Val-Ala-Cys-Asn-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-# (SEQ ID NO:66)

Name: Ca3.5
Species: caracteristicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTAACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCATGACCGCCTTCCAACTGAAAATCATCCCTTATATGATC
CCGTCAAACGGTGTTGCGATGATTCGGAATGCGACTATTCTTGCTGGCCTTGCTGTA
TGTTTGGATAACCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAAC
GATTGCAGT (SEQ ID NO:67)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLHDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCMFG (SEQ ID NO:68)

Toxin Sequence:
Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Met-Phe-# (SEQ ID NO:69)

Name: Ca3.6
Species: caracteristicus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTAAG
CAGGACGTTTCATCTGAACAGCATCCCTTCTTTGATCCCGTCAAACGGTGTTGCCGC
CGGTGTTACATGGGATGCATCCCTTGTTGCTTTTAACGTGTTGATGACCAACTTTCTC
GAG (SEQ ID NO:70)

Translation:
GSMMSKLGVLLTICLLLFPLTAVPLDGDQPADRPAERKQDVSSEQHPFFDPVKRCCRRC
YMGCIPCCF (SEQ ID NO:71)

Toxin Sequence:

Cys-Cys-Arg-Arg-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:72)

Name: Cr3.1
Species: circumcisus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGGGTATTGTTGACCATCT
GTCTGCTTCTGTTTCCCCTTACTGCTCTTCCAATGGATGGAGATCAACCTGCAGACC
AACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATA
AGAGACGAAAGTGTTGCGGCAAAGACGGGCCATGCCCCAAATATTTCAAAGACAAT
TTTATTTGTGGTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCGTTATCACGAT
TCGCCAAGTGTCTTAATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:73)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQDDISSEQYPLFDKRRKCCGKD
GPCPKYFKDNFICGCC (SEQ ID NO:74)

Toxin Sequence:
Arg-Lys-Cys-Cys-Gly-Lys-Asp-Gly-Xaa3-Cys-Xaa3-Lys-Xaa5-Phe-Lys-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:75)

Name: Da3.1
Species: dalli
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTAACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCAGGACCGCCTTCCAACTGAAAATCATCCCTTATATGATC
CCGTCAAACGGTGTTGCGATGATTCGGAATGCGACTATTCTTGCTGGCCTTGCTGTA
TTTTATCATAACCTTTGTTATCGCGGCCTCATCAAGTGTCAAATGAATAAGTAAAAT
GATTGCAGT (SEQ ID NO:76)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCILS (SEQ ID NO:77)

Toxin Sequence:
Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Ile-Leu-Ser-^ (SEQ ID NO:78)

Name: Da3.2
Species: dalli
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATTTG
TCTACTTCTGTTTCCCCTTACTGCTGTTCCACTGGATGGAGATCAGCCTGCAGACCG
ACCTGCAGAGCGTATGCAGGACGGCATTTCATCTGAACATCATCCATTTTTTGATTC
CGTCAAAAAGAAACAACAGTGTTGCCCGCCGGTGGCATGCAACATGGGATGCGAGC
CTTGTTGTGGATGACCAGCTTTGTTATCGCGGCTCATGAAGTGTCCTAATGAATAAG
TAAAACGATTGCAGT (SEQ ID NO:79)

Translation:
MMSKLGVLLTICLLLFPLTAVPLDGDQPADRPAERMQDGISSEHHPFFDSVKKKQQCCP
PVACNMGCEPCCG (SEQ ID NO:80)

Toxin Sequence:
Xaa2-Gln-Cys-Cys-Xaa3-Xaa3-Val-Ala-Cys-Asn-Met-Gly-Cys-Xaa1-Xaa3-Cys-Cys-# (SEQ ID NO:81)

Name: Da3.3
Species: dalli
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGATCATATG
TCTATTTCTGTTTCCCCTTACTGCTGTTCAGCTCAATGGAGATCAGCCTGCAGACCAA
TCTGCAGAGCGTATGCAGGACAAAATTTCATCTGAACATCATCCCTTTTTTGATCCC
GTCAAACGTTGTTGCAACGCGGGGTTTTGCCGCTTCGGATGCACGCCTTGTTGTTGG
TGACCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAATGATTG
CAGT (SEQ ID NO:82)

Translation:
MMSKLGVLLIICLFLFPLTAVQLNGDQPADQSAERMQDKISSEHHPFFDPVKRCCNAGFC
RFGCTPCCW (SEQ ID NO:83)

Toxin Sequence:
Cys-Cys-Asn-Ala-Gly-Phe-Cys-Arg-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID NO:84)

Name: Di3.1
Species: distans
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGCTGACCATCTT
TCTGCTTCTGTTTCCCCTTACTGCTGTTCCGCTGGATGGAGATCAACCCGCAGACGG
ACTTGCAGAGCGCATGCAGGACGACAGTTCAGCTGCACTGATTAGAGACTGGCTTC
TTCAAACCCGACAGTGTTGTGTGCATCCATGCCCATGCACGCCTTGCTGTAGATGAC
CAGCTTTGTCATCGCGGCTACGTCAAGTATCTAATGAATAAGTAAGTAAAACGATTG

CAGT (SEQ ID NO:85)

Translation:
MMSKLGVLLTIFLLLFPLTAVPLDGDQPADGLAERMQDDSSAALIRDWLLQTRQCCVHP
CPCTPCCR (SEQ ID NO:86)

Toxin Sequence:
Xaa2-Cys-Cys-Val-His-Xaa3-Cys-Xaa3-Cys-Thr-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:87)

Name: E3.1
Species: ermineus
Cloned: Yes

DNA Sequence:
ACCTCAAGAGGGATCGATCGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACC
ATCTGTCTGCTTCTGTTTCCCATTACTGCTCTTCTGATGGATGGAGATCAGCCTGCAG
ACCGACCTGCAGAGCGTACGGAGGATGACATTTCATCTGACTACATTCCCTGTTGCA
GTTGGCCATGCCCCCGATACTCCAACGGTAAACTTGTTTGTTTTTGTTGCCTTGGATG
ATAATGTGTTGATGACCAACTTTGTTATCACGGCTACGTCAAGTGTCTACTGAATAA
GTAAAATGATTGCAGTA (SEQ ID NO:88)

Translation:
MMSKLGALLTICLLLFPITALLMDGDQPADRPAERTEDDISSDYIPCCSWPCPRYSNGKL
VCFCCLG (SEQ ID NO:89)

Toxin Sequence:
Cys-Cys-Ser-Xaa4-Xaa3-Cys-Xaa3-Arg-Xaa5-Ser-Asn-Gly-Lys-Leu-Val-Cys-Phe-Cys-Cys-
Leu-# (SEQ ID NO:90)

Name: Ge3.2
Species: generalis
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGGTTCTGTTTCCCC
TTACTGCTCTTCCACTGGATGGAGAACAACCTGTAGACCGACATGCCGAGCATATGC
AGGATGACAATTCAGCTGCACAGAACCCCTGGGTTATTGCCATCAGACAGTGTTGC
ACGTTCTGCAACTTTGGATGCCAACCTTGTTGCCTCACCTGATAACGTGTTGATGAC
CAACTTTCTCGAG (SEQ ID NO:91)

Translation:
GSMMSKLGVLLTICLVLFPLTALPLDGEQPVDRHAEHMQDDNSAAQNPWVIAIRQCCTF
CNFGCQPCCLT (SEQ ID NO:92)

Toxin Sequence:
Xaa2-Cys-Cys-Thr-Phe-Cys-Asn-Phe-Gly-Cys-Gln-Xaa3-Cys-Cys-Leu-Thr-^ (SEQ ID NO:93)

Name: Ge3.3
Species: generalis
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGGTTCTGTTTCCCC
TTACTGCTCTTCCACTGGATGGAGAACAACCTGTAGACCGACATGCCGAGCATATGC
AGGATGACAATTCAGCTGCACAGAACCCCTGGGTTATTGCCATCAGACAGTGTTGC
ACGTTCTGCAACTTTGGATGCCAGCCTTGTTGCGTCCCCTGATAACGTGTTGATGAC
CAACTTTCTCGAG (SEQ ID NO:94)

Translation:
GSMMSKLGVLLTICLVLFPLTALPLDGEQPVDRHAEHMQDDNSAAQNPWVIAIRQCCTF
CNFGCQPCCVP (SEQ ID NO:95)

Toxin Sequence:
Xaa2-Cys-Cys-Thr-Phe-Cys-Asn-Phe-Gly-Cys-Gln-Xaa3-Cys-Cys-Val-Xaa3-^ (SEQ ID NO:96)

Name: μ-GIIIA
Species: geographus
Cloned: Yes

DNA Sequence:
GTCGACTCTAGAGGATCCGACAACAAAGAGTCAACCCCACTGCCACGTCAAGAGCG
AAGCGCCACAGCTAAGACAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGG
AGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGA
GATGAACCTGCAAACCGACCTGTCGAGCGTATGCAGGACAACATTTCATCTGAGCA
GTATCCCTTGTTTGAGAAGAGACGAGATTGTTGCACTCCGCCGAAGAAATGCAAAG
ACCGACAATGCAAACCCCAGAGATGTTGCGCTGGACGATAACGTGTTGATGACCAA
CTTTATCACGGCTACGTCAAGTGTTTAGTGAATAAGTAAAATGATTGCAGTCTTGCT
CAGATTTGCTTTTGTGTTTTGGTCTAAAGATCAATGACCAAACCGTTGTTTTGATGCG
GATTGTCATATATTTCTCGATTCCAATCCAACACTAGATGATTTAATCACGATAGAT
TAATTTTCTATCAATGCCTTGATTTTTCGTCTGTCATATCAGTTTTGTTTATATTTATT
TTTTCGTCACTGTCTACACAAACGCATGCATGCACGCATGCACGCACACACGCACGC
ACGCTCGCACAAACATGCGCGCGCACGCACACACACACACACACACACACAAACACA
CACACAAGCAATCACACAATTATTGACATTATTTATTTATTCATTGATGTATTTGTTA
TTCGTTTGCTTGTTTTTAGAATAGTTTGAGGCCGTCTTTTTGGATTTATTTGAACTGC
TTTATTGTATACGAGTACTTCGTGCTTTGAAACACTGCTGAAAATAAAACAAACACT
GACGTAGC (SEQ ID NO:97)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPK
KCKDRQCKPQRCCAGR (SEQ ID NO:98)

Toxin Sequence:

Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Gln-Cys-Lys-Xaa3-Gln-Arg-Cys-Cys-Ala-# (SEQ ID NO:99)

Name: μ-GIIIB
Species: geographus
Isolated: Yes
Cloned: Yes

DNA Sequence:
GGCCAGACGACAACAAAGAGTCAACCCCACTGCCACGTCAAGAGCGAAGCGCCAC
AGCTAAGACAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTT
GACCATCTGTCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATGAACCT
GCAAACCGACCTGTCGAGCGTATGCAGGACAACATTTCATCTGAGCAGTATCCCTTG
TTTGAGAAGAGACGAGATTGTTGCACTCCGCCGAGGAAATGCAAAGACCGACGATG
CAAACCCATGAAATGTTGCGCTGGACGATAACGTGTTGATGACCAACTTTATCACG
GCTAGCTCAGTGTTTAGTGAATAAGTAAAATGATTGCAGTCTTGCTCAGATTGCTTT
TGTGTTTTGGTCTAAGATCAATGACCAAACCGTTGTTTTGATGCGGATTGTCATATA
TTTCTCGATTCCAATCCAACACTAGATGATTTAATCACGATAGATTAATTTTCTATCA
ATGCCTTGATTTTTCGTCTGTCATATCAGTTTTGTTTATATTTATTTTTTCGTCACTGT
CTACACAAACGCATGCATGCACGCATGCACGCACACACGCACGCACGCTCGCACAA
ACATGCGCGCGCACGCACACACACACACACACACACAAACACACACACGAAGCAATC
ACACAATTAGTTGACATTATTTATTTATTCATTGATGTATTTGTTATTCGTTTGCTTGT
TTTTAGAATAGTTTGAGGCCGTCTTTTTGGATTTATTTGAACTGCTTTATTGTATACG
AGTACTTCGTGCTTTGAAACACTGCTGAAAATAAAACAAACACTGACGTAGCAAAA
AAAAAAA (SEQ ID NO:100)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPRK
CKDRRCKPMKCCAGR (SEQ ID NO:101)

Toxin Sequence:
Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Arg-Cys-Lys-Xaa3-Met-Lys-Cys-Cys-Ala-# (SEQ ID NO:102)

Name: μ-GIIIC
Species: geographus
Isolated: Yes

Toxin Sequence:

Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Arg-Cys-Lys-Xaa3-Leu-Lys-Cys-Cys-Ala-# (SEQ ID NO:103)

Name: Gm3.1
Species: gloriamaris

Cloned: Yes

DNA Sequence:
CTCACTATAGGAATTCGAGCTCGGTACACGGGATCGATAGCAGTTCATGATGTCTAA
ACTGGGAGCCTTGTTGACCATCTGTCTACTTCTGTTTTCCCTAACTGCTGTTCCGCTG
GATGGAGATCAACATGCAGACCAACCTGCAGAGCGTCTGCATGACCGCCTTCCAAC
TGAAAATCATCCCTTATATGATCCCGTCAAACGGTGTTGCGATGATTCGGAATGCGA
CTATTCTTGCTGGCCTTGCTGTATGTTTGGATAACCTTTGTTATCGCGGCCTCGATAA
GTGTCTAATGAATAAGTAAAACGATTGCAGTAGGC (SEQ ID NO:104)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLHDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCMFG (SEQ ID NO:105)

Toxin Sequence:
Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Met-Phe-# (SEQ ID NO:106)

Name: Gm3.2
Species: gloriamaris
Cloned: Yes

DNA Sequence:
GTTCATGATGTCTAAACTGGGAGTCTTGTTGATCATCTGTCTACTTCTGTTTCCCCTT
ACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGATATGCAGAGCGTATGCA
GGACGACATTTCATCTGAACATCATCCCATGTTTGATGCCGTCAGAGGGTGTTGCCA
TCTGTTGGCATGCCGCTTCGGATGCTCGCCTTGTTGTTGGTGATCAGCTTTGTTATCG
CGGCCTCATCAAGTGACTCTAATGCAAA (SEQ ID NO:107)

Translation:
MMSKLGVLLIICLLLFPLTAVPLDGDQPADRYAERMQDDISSEHHPMFDAVRGCCHLLA
CRFGCSPCCW (SEQ ID NO:108)

Toxin Sequence:
Gly-Cys-Cys-His-Leu-Leu-Ala-Cys-Arg-Phe-Gly-Cys-Ser-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID NO:109)

Name: Gm3.3
Species: gloriamaris
Cloned: Yes

DNA Sequence:
GAGACGACAAGGAACAGTCAACCCCACAGCCACGCCAAGAGCAGACAGCCACAGC
TACGTGAAGAAGGGTGGAGAGAGGTTCGTGATGTTGAAAATGGGAGTGGTGCTATT
CATCTTCCTGGTACTGTTTCCCCTGGCAACGCTCCAGCTGGATGCAGATCAACCTGT
AGAACGATATGCGGAGAACAAACAGCTCCTCAACCCAGATGAAAGGAGGGAAATC

ATATTGCATGCTCTGGGGACGCGATGCTGTTCTTGGGATGTGTGCGACCACCCGAGT
TGTACTTGCTGCGGCGGTTAGCGCCGAACATCCATGGCGCTGTGCTGGGCGGTTTTA
TCCAACAACGACAGCGTTTGTTGATTTCATGTATCATTGCGCCCACGTCTCTTGTCTA
AGAATGACGAACATGATTGCACTCTGGTTCAGATTTCGTGTTCTTTTCTGACAATAA
ATGACAAAACTCCAAAAAA (SEQ ID NO:110)

Translation:
MLKMGVVLFIFLVLFPLATLQLDADQPVERYAENKQLLNPDERREIILHALGTRCCSWD
VCDHPSCTCCGG (SEQ ID NO:111)

Toxin Sequence:
Cys-Cys-Ser-Xaa4-Asp-Val-Cys-Asp-His-Xaa3-Ser-Cys-Thr-Cys-Cys-Gly-# (SEQ ID NO:112)

Name: La3.1
Species: laterculatus
Cloned: Yes

DNA Sequence:
CGACCTCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGA
CCATCTGTCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAACCTGC
AGACCGACCTGCAGAGCGTATGCAGGACGTTTCATCTGAACAGCATCCCTTGTATG
ATCCCGTCAAACGGTGTTGCGACTGGCCATGCAGCGGATGCATCCCTTGTTGCTAAT
AGTAACAACGTGTTGATAACCAACTTTCTTACCACGACTACGTCAAGTGTCTAATGA
ATAAGTAAAATGATTGCAGT (SEQ ID NO:113)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADRPAERMQDVSSEQHPLYDPVKRCCDWPC
SGCIPCC (SEQ ID NO:114)

Toxin Sequence:
Cys-Cys-Asp-Xaa4-Xaa3-Cys-Ser-Gly-Cys-Ile-Xaa3-Cys-Cys-^ (SEQ ID NO:115)

Name: La3.2
Species: laterculatus
Cloned: Yes

DNA Sequence:
CGACCTCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGA
CCATCTGTCTGCTTCTGTTTCCCCTTACTGCTCTGGATGGAGATCAACCTGCAGACC
GACTTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCAGCATCCCTTTGAAAAG
AGACGAGACTGTTGCACACCTCCGAAGAAATGCAGAGACCGACAATGCAAACCTGC
ACGTTGTTGCGGAGGATAACGTGTTGATGACCAACTTTGTTATCACGGCTACGTCAA
GTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:116)

Translation:
MMSKLGVLLTICLLLFPLTALDGDQPADRLAERMQDDISSEQHPFEKRRDCCTPPKKCR

DRQCKPARCCGG (SEQ ID NO:117)

Toxin Sequence:
Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Arg-Asp-Arg-Gln-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-# (SEQ ID NO:118)

Name: La3.3
Species: laterculatus
Cloned: Yes

DNA Sequence:
GGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGC
TTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAACTTGCACGCCGATCTGC
AGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATCACCTCTTTGAAAAGAGAC
GACCACCATGTTGCACCTATGACGGGAGTTGCCTAAAAGAATCATGCATGCGTAAA
GCTTGTTGCGGATGATAACGTGTTGATGACCAACTTTGTTATCACGGCTACTCAAGT
GTCTAATGAATAAGTAAAATGATTGCAGTA (SEQ ID NO:119)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQLARRSAERMQDNISSEQHHLFEKRRPPCCTYD
GSCLKESCMRKACCG (SEQ ID NO:120)

Toxin Sequence:
Arg-Xaa3-Xaa3-Cys-Cys-Thr-Xaa5-Asp-Gly-Ser-Cys-Leu-Lys-Xaa1-Ser-Cys-Met-Arg-Lys-Ala-Cys-Cys-# (SEQ ID NO:121)

Name: La3.3A
Species: laterculatus
Cloned: Yes

DNA Sequence:
GGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCACCTGTCTGC
TTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAACTTGCACGCCGACCTG
CAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGAAAGGAGA
CGACCACCATGTTGCACCTATGACGGGAGTTGCCTAAAAGAATCATGCAAGCGTAA
AGCTTGTTGCGGATAATAACGTGTTGATGACCAACTTTGTTATCACGGCTACTCAAG
TGTCTAATGAATAAGTAAAATGATTGCAGTA (SEQ ID NO:122)

Translation:
MMSKLGVLLTTCLLLFPLTALPMDGDQLARRPAERMQDNISSEQHPFFERRRPPCCTYD
GSCLKESCKRKACCG (SEQ ID NO:123)

Toxin Sequence:
Arg-Xaa3-Xaa3-Cys-Cys-Thr-Xaa5-Asp-Gly-Ser-Cys-Leu-Lys-Xaa1-Ser-Cys-Lys-Arg-Lys-Ala-Cys-Cys-# (SEQ ID NO:124)

Name: Lp3.1
Species: leopardus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCGTCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCGGCTGGTTGGAGATCAACCTGCAGAGCGACCTGCAAAGCGTACGC
AGGACGACATTCCAGATGGACAGCATCCGTTAAATGATAGGCAGATAAACTGTTGC
CCGTGGCCATGCCCTAGTACATGCCGCCATCAATGCTGCCATTAATGATAACGTGTT
GATGACCAACTTTCTCGAG (SEQ ID NO:125)

Translation:
GSMMSKLGVLLTVCLLLFPLTALRLVGDQPAERPAKRTQDDIPDGQHPLNDRQINCCPW
PCPSTCRHQCCH (SEQ ID NO:126)

Toxin Sequence:
Xaa2-Ile-Asn-Cys-Cys-Xaa3-Xaa4-Xaa3-Cys-Xaa3-Ser-Thr-Cys-Arg-His-Gln-Cys-Cys-His-^
(SEQ ID NO:127)

Name: Lv3.1
Species: lividus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCGTCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCGGCTGGTTAGAGATCAACCTGCAGAGCGACCTGCAAAGCGTACGC
AGGACGACATTCCAAATGGACAGGATCCGTTAATTGATAGGCAGATAAATTGTTGC
CCTTGGCCATGCCCTGATTCATGCCACTATCAATGCTGCCACTGATAACGTGTTGAT
GACCAACTTTCTCGAG (SEQ ID NO:128)

Translation:
GSMMSKLGVLLTVCLLLFPLTALRLVRDQPAERPAKRTQDDIPNGQDPLIDRQINCCPWP
CPDSCHYQCCH (SEQ ID NO:129)

Toxin Sequence:
Xaa2-Ile-Asn-Cys-Cys-Xaa3-Xaa4-Xaa3-Cys-Xaa3-Asp-Ser-Cys-His-Xaa5-Gln-Cys-Cys-His-^
(SEQ ID NO:130)

Name: L3.1
Species: lynceus
Cloned: Yes

DNA Sequence:
AAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTG

CTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAATCTGCAGACCGACTTG
CAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGAAAAGAGA
GGACGAGACTGTTGCACACCTCCGAGGAAATGCAGAGACCGAGCCTGCAAACCTCA
ACGTTGTTGCGGAGGATAAGCTGTTGATGACCAACTTTGTTATACGGC (SEQ ID
NO:131)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQSADRLAERMQDNISSEQHPFFEKRGRDCCTPP
RKCRDRACKPQRCCGG (SEQ ID NO:132)

Toxin Sequence:
Gly-Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Arg-Asp-Arg-Ala-Cys-Lys-Xaa3-Gln-Arg-
Cys-Cys-Gly-# (SEQ ID NO:133)

Name: M3.1
Species: magus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATGAACCTGCAAACCG
ACCTGTCGAGCGTATGCAGGACAACATTTCATCTGAGCAGTATCCCTTGTTTGAGAA
GAGACGAGATTGTTGCACTCCGCCGAAGAAATGCAAAGACCGACAATGCAAACCCC
AGAGATGTTGCGCTGGACGATAACGTGTTGATGACCAACTTTATCACGGCTACGTCA
AGTGTTTAGTGAATAAGTAAAATGATTGCAGTCTTGCTCAGATTTGCTTTTGTGTTTT
GGTCTAAAGATCAATGACCAAACCGTTGTTTTGATGCGGATTGTCATATATTTCTCG
ATTCCAATCCAACACTAGATGATTTAATCACGATAGATTAATTTTCTATCAATGCCT
TGATTTTTCGTCTGTCATATCAGTTTTGTTTATATTTATTTTTTCGTCACTGTCTACAC
AAACGCATGCATGCACGCATGCACGCACACACGCACGCACGCTCGCACAAACATGC
GCGCGCACGCACACACACACACACACACACACAAACACACACACGAAGCAATCACAC
AATTAGTTGACATTATTTATTTATTCATTGATGTATTTGTTATTCGTTTGCTTGTTTTT
AGAATAGTTTGAGGCCGTCTTTTTGGATTTATTTGAACTGCTTTATTGTATACGAGTA
CTTCGTGCGGGGAAACACTGCTGAAAATAAAACAAACACTGACGTAGCAAAAAAA
AAAAA (SEQ ID NO:134)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDEPANRPVERMQDNISSEQYPLFEKRRDCCTPPK
KCKDRQCKPQRCCAGR (SEQ ID NO:135)

Toxin Sequence:
Arg-Asp-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Gln-Cys-Lys-Xaa3-Gln-Arg-Cys-
Cys-Ala-# (SEQ ID NO:136)

Name: M3.2
Species: magus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCAATGGATGGAGATCAACCTGCAGACCA
ACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAT
GAGAAAAAGGTGTTGCGGCCCCGGCGGTTCATGCCCCGTATATTTCAGAGACAATT
TTATTTGTGGTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCATTATCACGAC
TACGCCAAGTGTCTAATGAATAAATAAAATGATTGCAGTCTCGCTCAGATTTGCTTT
TGTATTTTGGTCTAAAGATCAATGACCAAACCGTTGTTTTGGTGTGGATTTTCATATA
TTTCTCGAGTCCTATCCAACACTAGATGATTTAATCACGATAGATCTGATTTTTTTAT
CAAAGGCTTGGTTTTTCGTCTGTCACATCAGTTTTGTTTATATTTAATTTTTCGTCACT
GATTACACACACGCATGAACGCACAGAGTACTAACACATACACACACACACACACA
CACACACACACACACACACACACACACACACACACACACACACACGCGCGCGCGCGGCG
CCATCTAGTAGCGCCGCGACGACACACAC (SEQ ID NO:137)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQDDISSEQYPLFDMRKRCCGPG
GSCPVYFRDNFICGCC (SEQ ID NO:138)

Toxin Sequence:
Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Arg-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:139)

Name: M3.3
Species: magus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TTTGCTTCTGTTTCCCCTTACTGCTCTTCCGAGGGATGGAGATCAATCTGTAGACCGA
CCTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCTGCATCCCTTGTCAATCAGA
AAAAGAATGTGTTGCGGCGAGAGTGCGCCATGCCCCAGCTATTTCAGAAACAGTCA
GATTTGTCATTGTTGTTAAATGACAACGTGTCGATGACCACCTTCGTTATCACGACT
AATGATAAGTAAAATGATTGCAGTCTCGCTCAGATTTGCTTTTGTATTTTGGTCTAA
AGATCAATGACCAAACCGTTGTTTTGATGTGGATTTTCATATATTTCTCGAGTCCTAT
CCAACACTAGATGATTTAATCACGATAGATCTGATTTTTTTATCAAAGCCTTGGTTTT
TCGTCTGTCACATCAGTTTTGTTTATATTTAATTTTTCGTCACTGATTACACACACGC
ATGAACGCACAGACGTACTAACACATACACACACACACACACACACACACACACAC
ACACACACACACACACACACACAC (SEQ ID NO:140)

Translation:
MMSKLGVLLTICLLLFPLTALPRDGDQSVDRPAERMQDDISSELHPLSIRKRMCCGESAP
CPSYFRNSQICHCC (SEQ ID NO:141)

Toxin Sequence:
Met-Cys-Cys-Gly-Xaa1-Ser-Ala-Xaa3-Cys-Xaa3-Ser-Xaa5-Phe-Arg-Asn-Ser-Gln-Ile-Cys-His-Cys-Cys-^ (SEQ ID NO:142)

Name: M3.4
Species: magus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCAATGGATGGAGATCAACCTGCAGACCA
ACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAA
GAGACAAAAGTGTTGCGGCCCCGGCGGTTCATGCCCCGTATATTTCACAGACAATTT
TATTTGTGGTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCATTATCACGACT
ACGCCAAGTGTCTAATGAATAAATAAAATGATTGCAGTCTCGCTCAGATTTGCTTTT
GTATTTGGTCTAAAGATCAATGACCAAACCGTTGTTTTGGTGCTGGATTTTCATATA
TTTCTCGATTCCTATCCAACACTAGATGATTTAATCACGATAGATCTGATTTTTTTAT
CAATGCCTTAATTTTTTGCTCTGTCATATCAGTTTTGTTTATAT (SEQ ID NO:143)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCGPGG
SCPVYFTDNFICGCC (SEQ ID NO:144)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Thr-Asp-Asn-Phe-Ile-Cys-
Gly-Cys-Cys-^ (SEQ ID NO:145)

Name: M3.5
Species: magus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCAATGGATGGAGATCAACCTGCAGACCA
ACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAA
GAGACAAAAGTGTTGCGGCCCCGGCGGTTCATGCCCCGTATATTTCAGAGACAATTT
TATTTGTGGTTGTTGTTAAATGACAACGTGTCGATGACCATCTTCATTATCACGACT
ACGCCAAGTGTCTAATGAATAAATAAAATGATTGCAGTCTCGCTCAGATTTGCTTTT
GTATTTTGGTCTAAAGATCAATGACCAAACCGTTGTTTTGGTGTGGATTTTCATATAT
TTCTCGATTCCTATCCAACACTAGATGATTTAATCACGATAGATCTGATTTTTT (SEQ
ID NO:146)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCGPGG
SCPVYFRDNFICGCC (SEQ ID NO:147)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Gly-Xaa3-Gly-Gly-Ser-Cys-Xaa3-Val-Xaa5-Phe-Arg-Asp-Asn-Phe-Ile-Cys-
Gly-Cys-Cys-^ (SEQ ID NO:148)

Name: U001
Species: magus
Isolated: No

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Ser-Gly-Gly-Ser-Cys-Xaa3-Leu-Xaa5-Phe-Arg-Asp-Arg-Leu-Ile-Cys-Xaa3-Cys-Cys-^ (SEQ ID NO:149)

Name: Comatose/Death
Species: marmoreus
Isolated: Yes

Toxin Sequence:
Ser-Lys-Gln-Cys-Cys-His-Leu-Ala-Ala-Cys-Arg-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-Asn-^ (SEQ ID NO:150)

Name: Mr3.1
Species: marmoreus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCGTTACTGCTCTTCCGATGGATGGTGATCAACCTGCAGACCGA
CTTGTAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGAAAAG
AGAAGAGGAGGCTGTTGCACACCTCCGAGGAAATGCAAAGACCGAGCCTGCAAAC
CTGCACGTTGCTGCGGCCCAGGATAACGTGTTGATGACCAACTTTGTTATCACGGCT
ACGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAG (SEQ ID NO:151)

Translation:
MMSKLGVLLTICLLLFPVTALPMDGDQPADRLVERMQDNISSEQHPFFEKRRGGCCTPP
RKCKDRACKPARCCGPG (SEQ ID NO:152)

Toxin Sequence:
Arg-Gly-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:153)

Name: Mr3.2
Species: marmoreus
Cloned: Yes

DNA Sequence:
GAGCTCGGTACCCCGACCTCAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTG
GGAATCTTGTTGACCATCTGTCTACTTCTATTTCCCCTTACTGCTGTTCCGCTGGATG

GAGATCAACCTGCAGACCGACCTGCAGAGCGTATGCAGGACGACATTTCATCTGAA
CATCATCCCTTTTTTGATCCCGTCAAACGGTGTTGCAGGTTATCATGCGGCCTGGGA
TGCCACCCTTGTTGTGGATGACCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAAT
GAATAAGTAAAA (SEQ ID NO:154)

Translation:
MMSKLGILLTICLLLFPLTAVPLDGDQPADRPAERMQDDISSEHHPFFDPVKRCCRLSCG
LGCHPCCG (SEQ ID NO:155)

Toxin Sequence:
Cys-Cys-Arg-Leu-Ser-Cys-Gly-Leu-Gly-Cys-His-Xaa3-Cys-Cys-# (SEQ ID NO:156)

Name: Mr3.3
Species: marmoreus
Cloned: Yes

DNA Sequence:
GGCCTACACCAAGCTTGCATGCCTGCAGGTCGACTCTAGAGGATCCCCGATCGATA
GCAGTTCATGATGTCTAGACTGGGAGTCTTGTTGACCATCTGTCTACTTCTGTTTCCC
CTTACTGCTGTTCCGCTGGATGGAGATCAACCTGCGGACCGACCTGCAGAGCGCCTG
CAGGACGACATTTCATCTGAACATCATCCCCATTTTGATTCCGGCAGAGAGTGTTGC
GGTTCGTTCGCATGCCGCTTTGGATGCGTGCCTTGTTGTGTATGACCAGCTTTGTTAT
CACGGCCTCATCGAGTGTCTAATGAATAAGTAAAACGATTGCAGTAGGCGGGTACC
GAGCTCGAATTCC (SEQ ID NO:157)

Translation:
MMSRLGVLLTICLLLFPLTAVPLDGDQPADRPAERLQDDISSEHHPHFDSGRECCGSFAC
RFGCVPCCV (SEQ ID NO:158)

Toxin Sequence:
Xaa1-Cys-Cys-Gly-Ser-Phe-Ala-Cys-Arg-Phe-Gly-Cys-Val-Xaa3-Cys-Cys-Val-^ (SEQ ID NO:159)

Name: Mr3.4
Species: marmoreus
Cloned: Yes

DNA Sequence:
CGACCTCAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGA
CCATCTGTCTACTTCTATTTCCCCTTACTGCTGTTCCGCTGGATGGAGACCAACCTGC
AGACCGACCTGCAGAGCGTATGCAGGACGACATTTCATCTGAACGTCATCCTTTTTT
TGATCGCAGCAAACAGTGTTGCCATCTGCCGGCATGCCGCTTCGGATGTACGCCTTG
TTGTTGGTGATCAGCTTTGTTATCGCGTCCTCATCAAGTGTCTAATGAATAAGTAAA
ATGATTGCAG (SEQ ID NO:160)

Translation:

MMSKLGVLLTICLLLFPLTAVPLDGDQPADRPAERMQDDISSERHPFFDRSKQCCHLPAC
RFGCTPCCW (SEQ ID NO:161)

Toxin Sequence:
Ser-Lys-Gln-Cys-Cys-His-Leu-Xaa3-Ala-Cys-Arg-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-Xaa4-^
(SEQ ID NO:162)

Name: Mr3.5
Species: marmoreus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCGCTGGATGGAGATCAACCTGCAGACCAACGTGCAGAGCGTACG
CAGGCCGAGAAGCATTCCTTGCCTGATCCGAGAATGGGCTGTTGCCCGTTTCCATGC
AAAACCAGTTGCACTACTTTGTGTTGCGGGTGATGATAACGTGTTGATGACCAACTT
TCTCGAG (SEQ ID NO:163)

Translation:
GSMMSKLGVLLTICLLLFPLTALPLDGDQPADQRAERTQAEKHSLPDPRMGCCPFPCKT
SCTTLCCG (SEQ ID NO:164)

Toxin Sequence:
Met-Gly-Cys-Cys-Xaa3-Phe-Xaa3-Cys-Lys-Thr-Ser-Cys-Thr-Thr-Leu-Cys-Cys-# (SEQ ID
NO:165)

Name: U014
Species: marmoreus
Isolated: Yes

Toxin Sequence:
Cys-Cys-His-Xaa4-Asn-Xaa4-Cys-Asp-His-Leu-Cys-Ser-Cys-Cys-Gly-Ser-^ (SEQ ID NO:166)

Name: U017
Species: marmoreus
Cloned: Yes

DNA Sequence:
GCCAAGCTTGCATGCCTGCAGGATGACTCTAGAGGATCCCCACCTCAAGAGGGATC
GATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTACTTCTGTT
TGCCCTTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAACG
TATGCAGGACGACATTTCATCTGAACGTCATCCCATGTTTGATGCCGTCAGAGATTG
TTGCCCGTTGCCGGCATGCCCCTTTGGATGCAACCCTTGTTGTGGATGACCAGCTTT
GTTATCGGGACCTCATCAAGTGTCTAATGAATAAGTAAAAAACGATTCGAGTGGGT
ACCGAGCTCGAATTCC (SEQ ID NO:167)

Translation:
MMSKLGVLLTICLLLFALTAVPLDGDQPADRPAERMQDDISSERHPMFDAVRDCCPLPA CPFGCNPCCG (SEQ ID NO:168)

Toxin Sequence:
Asp-Cys-Cys-Xaa3-Leu-Xaa3-Ala-Cys-Xaa3-Phe-Gly-Cys-Asn-Xaa3-Cys-Cys-# (SEQ ID NO:169)

Name: U019
Species: marmoreus
Isolated: Yes

Toxin Sequence:
Cys-Cys-Ala-Xaa3-Ser-Ala-Cys-Arg-Leu-Gly-Cys-Arg-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:170)

Name: U020
Species: marmoreus
Isolated: Yes

Toxin Sequence:
Cys-Cys-Ala-Xaa3-Ser-Ala-Cys-Arg-Leu-Gly-Cys-Arg-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:171)

Name: U022
Species: marmoreus
Isolated: Yes

Toxin Sequence:
Cys-Cys-Ala-Xaa3-Ser-Ala-Cys-Arg-Leu-Gly-Cys-Arg-Xaa3-Cys-Cys-Arg-^ (SEQ ID NO:172)

Name: U024
Species: marmoreus
Isolated: Yes

Toxin Sequence:
Gly-Cys-Cys-Gly-Ser-Phe-Ala-Cys-Arg-Phe-Gly-Cys-Val-Xaa3-Cys-Cys-Val-^ (SEQ ID NO:173)

Name: Nb3.1
Species: nobilis
Cloned: Yes

DNA Sequence:

GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTACTTCTGTTTCCCC
TTACTGCTCTTCCGCTGGATGAAGATCAACCGGTACACCGACCTGCAGAGCGTATGC
AGGACATTTCATCTGATCAACATCTCTTCTTTGATCTCATCAAACGGTGCTGCGAGT
TGCCATGCGGGCCAGGCTTTTGCGTCCCTTGTTGCTGACATCAATAACGTGTTGATG
ACCAACTTTCTCGAG (SEQ ID NO:174)

Translation:
GSMMSKLGVLLTICLLLFPLTALPLDEDQPVHRPAERMQDISSDQHLFFDLIKRCCELPCG
PGFCVPCC (SEQ ID NO:175)

Toxin Sequence:
Cys-Cys-Xaa1-Leu-Xaa3-Cys-Gly-Xaa3-Gly-Phe-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:176)

Name: Nb3.2
Species: nobilis
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTACTTCTGTTTCCCC
TTACTGCTTTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCAGATCGTATGC
AGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAAGAGACAAAAGTGTTGCA
CTGGGAAGAAGGGGTCATGCTCCGGCAAAGCATGCAAAAATCTCAAATGTTGCTCT
GGACGATAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:177)

Translation:
GSMMSKLGVLLTICLLLFPLTAFPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCTG
KKGSCSGKACKNLKCCSGR (SEQ ID NO:178)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-Cys-
Cys-Ser-# (SEQ ID NO:179)

Name: Pu3.1
Species: pulicarius
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTTTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
AGGACATTGCAACTGAACAGCATCCCTTCTTTGATCCCGTCAAACGGTGTTGCAACA
GCTGTTACATGGGATGCATCCCTTGTTGCTTCTAGTAATAACGTGTTGATGACCAAC
TTTCTCGAG (SEQ ID NO:180)

Translation:
GSMMSKLGVLLTICLLLFPLTAVPLDGDQPADRPAERMQDIATEQHPFFDPVKRCCNSC
YMGCIPCCF (SEQ ID NO:181)

Toxin Sequence:
Cys-Cys-Asn-Ser-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:182)

Name: Qc3.1
Species: quercinus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACAGCTCTTCAGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTACG
CAGGACATTGCATCTGAACAGTATCGAAAGTTTGATCAGAGACAGAGGTGTTGCCA
GTGGCCATGCCCCGGTAGTTGCAGATGCTGCCGTACTGGTTAACGTGTTGATGACCA
ACTTTCTCGAG (SEQ ID NO:183)

Translation:
GSMMSKLGVLLTICLLLFPLTALQLDGDQPADRPAERTQDIASEQYRKFDQRQRCCQWP
CPGSCRCCRTG (SEQ ID NO:184)

Toxin Sequence:
Xaa2-Arg-Cys-Cys-Gln-Xaa4-Xaa3-Cys-Xaa3-Gly-Ser-Cys-Arg-Cys-Cys-Arg-Thr-# (SEQ ID NO:185)

Name: QcIIIA
Species: quercinus
Isolated: Yes

Toxin Sequence:
Cys-Cys-Ser-Gln-Asp-Cys-Leu-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Asn-# (SEQ ID NO:186)

Name: QcIIIB
Species: quercinus
Isolated: Yes

Toxin Sequence:
Cys-Cys-Ser-Arg-His-Cys-Xaa4-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Asn-? (SEQ ID NO:187)

Name: R3.1
Species: radiatus
Isolated: Yes
Cloned: Yes

DNA Sequence:
TCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCT

GTCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAACCTGTAGACCG
ACTTGCAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATACCTTCTTTGAAAA
GAGACTACCATCGTGTTGCTCCCTTAACTTGCGGCTTTGCCCAGTACCAGCATGCAA
ACGTAACCCTTGTTGCACAGGATAACGTGTTGATGACCAACTTTGTTATCACGGCTA
CGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:188)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPVDRLAERMQDNISSEQHTFFEKRLPSCCSLNL
RLCPVPACKRNPCCTG (SEQ ID NO:189)

Toxin Sequence:
Leu-Xaa3-Ser-Cys-Cys-Ser-Leu-Asn-Leu-Arg-Leu-Cys-Xaa3-Val-Xaa3-Ala-Cys-Lys-Arg-Asn-Xaa3-Cys-Cys-Thr-# (SEQ ID NO:190)

Name: R3.2
Species: radiatus
Cloned: Yes

DNA Sequence:
AGGTCGACTCTAGAGGATCCCCAAGGATCGATAGCAGTTCATGATGTCTAAACTGG
GAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGG
AGATCAACCTGCAGACCGACTTGCAGAGCGTATGCAGGACGACATTTCATCTGAGC
AGCATCCCTTCTTTAAAAAGAGACAACAAAGATGTTGCACCGTTAAGAGGATTTGT
CCAGTACCAGCATGCAGAAGTAAACCTTGTTGCAAATCATAACGTATTGATGACCA
ACTTTGTTATCACGGCTACGTCAAGTGTCTAGTGAATAAGTAAAATGATTGCAG
(SEQ ID NO:191)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADRLAERMQDDISSEQHPFFKKRQQRCCTVK
RICPVPACRSKPCCKS (SEQ ID NO:192)

Toxin Sequence:
Xaa2-Gln-Arg-Cys-Cys-Thr-Val-Lys-Arg-Ile-Cys-Xaa3-Val-Xaa3-Ala-Cys-Arg-Ser-Lys-Xaa3-Cys-Cys-Lys-Ser-^ (SEQ ID NO:193)

Name: R3.3
Species: radiatus
Cloned: Yes

DNA Sequence:
ACCTCAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACC
ATCTGTCTGCTTCTGTTTCCCGTTACTGCTCTTCCGATGGATGGTGATCAACCTGCAG
ACCGACTTGTAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATCCCTTCTTTG
AAAAGAGAAGAGGAGGCTGTTGCACACCTCCGAGGAAATGCAAAGACCGAGCCTG
CAAACCTGCACGTTGCTGCGGCCCAGGATAACGTGTTGATGACCAACTTTGTTATCA
CGGCTACGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:194)

Translation:
MMSKLGVLLTICLLLFPVTALPMDGDQPADRLVERMQDNISSEQHPFFEKRRGGCCTPP
RKCKDRACKPARCCGPG (SEQ ID NO:195)

Toxin Sequence:
Arg-Gly-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:196)

Name: Ra3.1
Species: rattus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGGTGACCATCTGCCTGCTTCTGTTCCCT
CTTGCTGCTTTTCCACTGGATGGAGATCAACCTGCAGACCACCCTGCAAAGCGTACG
CAAGATGACAGTTCAGCTGCCCTGATCAATGCCTGGCTTGATGAATCCCAGACTTGC
TGCAGTAACTGCGGTGAAGATTGTGATGGTTGTTGCCAGTAACGTGTTGATGACCAA
CTTTCTCGAG (SEQ ID NO:197)

Translation:
GSMMSKLGVLVTICLLLFPLAAFPLDGDQPADHPAKRTQDDSSAALINAWLDESQTCCS
NCGEDCDGCCQ (SEQ ID NO:198)

Toxin Sequence:
Xaa2-Thr-Cys-Cys-Ser-Asn-Cys-Gly-Xaa1-Asp-Cys-Asp-Gly-Cys-Cys-Gln-^ (SEQ ID NO:199)

Name: Sm3.1
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:
GACCTCAAGAGGGATCGATAGCAGTTCGTGATGTCTAAACTGGGAGTCTTGTTGAC
CATCTGTCTGCTTCTGTTTCCTCTTACTGCTCTTCCGATGGATGGAGATCAACCTGCA
GACCAACCTGCAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTTGTTT
GATAAGAGACAAAAGTGTTGCACTGGGAAGAAGGGGTCATGCTCCGGCAAAGCAT
GCAAAAATCTCAAATGTTGCTCTGGACGATAACGTGTTGATGACCAACTTTGTTATC
ACGGCTACGTCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:200)

Translation:
MSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCTGKKG
SCSGKACKNLKCCSGR (SEQ ID NO:201)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-Cys-Cys-Ser-# (SEQ ID NO:202)

Name: U034
Species: stercusmuscarum
Isolated: Yes
Cloned: Yes

DNA Sequence:
GATCGATAGCAGTTCGTGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTT
CTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCA
GATCGTATGCAGAACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAAGAGACAA
AAGTGTTGCGGCCCCGGCGCGTCATGCCCCAGATATTTCAAAGACAATTTTATTTGT
GGTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCGTTATCACGACTTCGCCAA
GTGTCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:203)

Translation:
MSKLGVLLTICLLLFPLTALPMDGDQPADQPADRMQNDISSEQYPLFDKRQKCCGPGAS
CPRYFKDNFICGCC (SEQ ID NO:204)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Gly-Xaa3-Gly-Ala-Ser-Cys-Xaa3-Arg-Xaa5-Phe-Lys-Asp-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:205)

Name: S3.1
Species: striatus
Cloned: Yes

DNA Sequence:
CGACCTTTCAAGAGGGATCGATAGCAGTTCGCGATGTCTAAACTGGGGGTATTGTTG
ACCATCTGTCTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGAAGATCAACCTG
CAGACCAACTTGAAGATCGTATGCAGGACGACATTTCATCTGAGCAGTATCCCTCGT
TTGTTAGGAGACAAAAGTGTTGCGGCGAAGGCTCGTCATGCCCCAAATATTTCAAA
AACAATTTTATTTGTGGTTGTTGTTAAATGACAACGTGTCGATGACCAACTTCGTTA
TCACGACTACGCCAAGTGTCTTGTCTAATGATAATAAAATGATTCC (SEQ ID NO:206)

Translation:
MSKLGVLLTICLLLFPLTALPMDEDQPADQLEDRMQDDISSEQYPSFVRRQKCCGEGSSC
PKYFKNNFICGCC (SEQ ID NO:207)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Gly-Xaa1-Gly-Ser-Ser-Cys-Xaa3-Lys-Xaa5-Phe-Lys-Asn-Asn-Phe-Ile-Cys-Gly-Cys-Cys-^ (SEQ ID NO:208)

Name: S3.2
Species: striatus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCGTCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
AGGACGACATTTCATCTGACGAGCATCCCTTGTTTGATAAGAGACAAAACTGTTGCA
ATGGGGGATGCTCCAGCAAATGGTGCAGAGATCACGCACGTTGTTGCGGTCGATGA
TAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:209)

Translation:
GSMMSKLGVLLTVCLLLFPLTALPLDGDQPADRPAERMQDDISSDEHPLFDKRQNCCNG
GCSSKWCRDHARCCGR (SEQ ID NO:210)

Toxin Sequence:
Xaa2-Asn-Cys-Cys-Asn-Gly-Gly-Cys-Ser-Ser-Lys-Xaa4-Cys-Arg-Asp-His-Ala-Arg-Cys-Cys-#
(SEQ ID NO:211)

Name: Ts3.1
Species: tessulatus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATGTGTCTGCTTCTGTTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTAGG
CAGGACATTGCAACTGACGATCATCCTTTGTTTGATCCCGTCAAACGGTGCTGCCAC
AAATGCTATATGGGATGCATCCCTTGTTGCATTTAGTAACGTGTTGATGACCAACTT
TCTCGAG (SEQ ID NO:212)

Translation:
GSMMSKLGVLLTMCLLLFPLTAVPLDGDQPADRPAERRQDIATDDHPLFDPVKRCCHK
CYMGCIPCCI (SEQ ID NO:213)

Toxin Sequence:
Cys-Cys-His-Lys-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Ile-^ (SEQ ID NO:214)

Name: Ts3.2
Species: tessulatus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTGTGCTTCTGTTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCAACCTGCAGAGCGTACG
CAGAACGAGCAGCATCCCTTGTATGATCAGAAAAGAAAGTGTTGCCGGCCGCCATG
CGCCATGAGCTGCGGCATGGCTAGGTGTTGCTATTAATGATAACGTGTTGATGACCA
ACTTTCTCGAG (SEQ ID NO:215)

Translation:

GSMMSKLGVLLTICVLLFPLTAVPLDGDQPADQPAERTQNEQHPLYDQKRKCCRPPCA
MSCGMARCCY (SEQ ID NO:216)

Toxin Sequence:
Lys-Cys-Cys-Arg-Xaa3-Xaa3-Cys-Ala-Met-Ser-Cys-Gly-Met-Ala-Arg-Cys-Cys-Xaa5-^ (SEQ ID NO:217)

Name: Circling
Species: textile
Isolated: Yes
Cloned: Yes

DNA Sequence:
GAGTCAACCCACTGTCACGCCAAGAGCGGACGCCACAGCTAAGGCAAGAAGGATC
GATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCTGTCTACTTCTGT
TTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACCAACCTGCACAGC
GTCTGCAGGACCGCATTCCAACTGAAGATCATCCCTTATTTGATCCCAACAAACGGT
GTTGCCCGCCGGTGGCATGCAACATGGGATGCAAGCCTTGTTGTGGATGACCAGCTT
TGTTATCGCGGTCTCATGAAGTGTCTAATGAATAAGTAAAACGATTGCAGTTTCGTT
CAGATTTGCTGTTGTATTTTGGTCTAAAGATTAATGACCAAACTGTTCTTTTGATCCG
GATTTTCACGTATTTCTCGATTCCTATTCAACACTAGATAAGTTAATCACGACAGAT
CTGATTTTCCATCAATGCCTTGCTTTTTGGTCTGTCATATAAATCTTGTTTATATTTAA
TTTCTCGTCACTTTCAACACGCACACACACACACACACACACGCGCGCGC (SEQ ID NO:218)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAQRLQDRIPTEDHPLFDPNKRCCPPVA
CNMGCKPCCG (SEQ ID NO:219)

Toxin Sequence:
Cys-Cys-Xaa3-Xaa3-Val-Ala-Cys-Asn-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-Gly-^ (SEQ ID NO:220)

Name: Scratcher I
Species: textile
Cloned: Yes

DNA Sequence:
GGATCCAGACGACAAAGAAGAGTCAACCCACTGCCACGTCAAGAGCAGAGCCCAC
AGCTAAGACAAGAAGGATCGATAGCAGTTCATGATGTTTAAACTGGGAGTCTTGTT
GACCATCTGTCTCCTTCTGTTTTCCCTTAATGCTGTTCCGTTGGATGGAGATCAACCT
GCAGACCAACCTGCAGAGCGTCTGCTGGACGACATTTCATTTGAAAATAATCCCTTT
TATGATCCCGCCAAACGGTGTTGCAGGACTTGCTTCGGTTGCACACCTTGTTGTGGA
TGACCAGCCTCATCAAGTGTCTAACGAATAAGTAAAGCGATTGCAGTCTCGTTCAG
ATTTACTTTTGTATTCTGGTCTAAAGATTAATGACCAAACTCTTCTTTTGATCCGGAT
GTACATATATTTCTCGATTCCTATCCAACGCTAGATAAGCTAATCACGACAGATCTG

ATTTTCTGTCAATGCCTTGCTTTTTGGTCTCTCATATCACTCTTGTTTATATTTAATTT
CTCGTCACTATATATATATATACACACACACACACACGGAATTCCGATTGTCCAGTA
CCGTTCTTGGGATCGAGGTATTGCTGCGATGGCTTATTCTGTACTCTTTTCTTCTGCG
CTTGATAGTGATGTCTTCTACTCCCATCTGTGCTACCCCTGGCTTGATCTTTGATAGG
CGTGTGCCCTTCACTGGTTATAAACCCCTCTGATCCTACTCTCTGGACGCCTCGGGG
GCCCAACCTCCAAATAAAGCGACATCCAATGAAAAAA (SEQ ID NO:221)

Translation:
MMFKLGVLLTICLLLFSLNAVPLDGDQPADQPAERLLDDISFENNPFYDPAKRCCRTCFG
CTPCCG (SEQ ID NO:222)

Toxin Sequence:
Cys-Cys-Arg-Thr-Cys-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-# (SEQ ID NO:223)

Name: Tx3.1
Species: textile
Cloned: Yes

DNA Sequence:
GGAACAGTCAACCCCACAGCCACGCCAAGAGCAGACAGCCACAGCTACGTGAAGA
AGGGTGGAGAGAGGTTCATGATGTTGAAAATGGGAGTGGTGCTATTCATCTTTCTGG
TACTGTTTCCCCTGGCAACGCTCCAGCTGGATGCAGATCAACCTGTAGAACGATATG
CGGAGAACAAACAGCTCCTCAACCCAGATGAAAGGAGGGAAATCCTATTGCCTGCT
CTGAGGAAGTTCTGCTGTGATTCGAATTGGTGCCACATTTCGGATTGTGAGTGCTGC
TACGGTTAGCGCCGAACATCCATGGCACTGTGCTGGGCGGTTTCATCCCAACAACG
ACAGCGTTTGTTGATTTCATGTATCATTGCGCCCACGTCTCTTGTCTAAGAATGACG
AACATGATTGCACTCTGGTTCAGATTTCGTGTTCTTTTCTGACAATAAATGACAAAcC
TCC (SEQ ID NO:224)

Translation:
MMLKMGVVLFIFLVLFPLATLQLDADQPVERYAENKQLLNPDERREILLPALRKFCCDS
NWCHISDCECCYG (SEQ ID NO:225)

Toxin Sequence:
Phe-Cys-Cys-Asp-Ser-Asn-Xaa4-Cys-His-Ile-Ser-Asp-Cys-Xaa1-Cys-Cys-Xaa5-# (SEQ ID NO:226)

Name: U031
Species: textile
Isolated: Yes
Cloned: Yes

DNA Sequence:
CAAGGAACAGTCAACCCCACAGCCACGCCAAGAGCAGACAGCCACAGCTACGTGA
AGAAGGGTGGAGAGAGGTTCGTGATGTTGAAAATGGGAGTGGTGCTATTCATCTTC
CTGGTACTGTTTCCCCTGGCAACGCTCCAGCTGGATGCAGATCAACCTGTAGAACGA

TATGCGGAGAACAAACAGCTCCTCAGCCCAGATGAAAGGAGGGAAATCATATTGCA
TGCTCTGGGGACGCGATGCTGTTCTTGGGATGTGTGCGACCACCCGAGTTGTACTTG
CTGCGGTTAGCGCCGAACATCCATGGCGCTGTGCTGGGCGGTTTTATCCCAACAACG
ACAGCGTTTGTTGATTTCATGTATCATTGCGCCCACGTCTCTTGTCTAAGAATGACG
AACATGATTGCACTCTGGTTCAGATTTCGTGTTCTTTTCTGACAATAAATGACAAAA
CNCC (SEQ ID NO:227)

Translation:
MLKMGVVLFIFLVLFPLATLQLDADQPVERYAENKQLLSPDERREIILHALGTRCCSWD
VCDHPSCTCCG (SEQ ID NO:228)

Toxin Sequence:
Cys-Cys-Ser-Xaa4-Asp-Val-Cys-Asp-His-Xaa3-Ser-Cys-Thr-Cys-Cys-# (SEQ ID NO:229)

Name: U032
Species: textile
Isolated: Yes
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCGCTGGATGGAGATCAACCCGCAGACCAAGCTGCAGAGCGTATG
CAGGCCGAGCAGCATCCCTTGTTTGATCAGAAAAGACGGTGCTGCAAGTTTCCATG
CCCCGATAGTTGCAGATATTTGTGTTGCGGGTGATGATAACGTGTTGATGACCAACT
TTCTCGAG (SEQ ID NO:230)

Translation:
GSMMSKLGVLLTICLLLFPLTALPLDGDQPADQAAERMQAEQHPLFDQKRRCCKFPCPD
SCRYLCCG (SEQ ID NO:231)

Toxin Sequence:
Arg-Cys-Cys-Lys-Phe-Xaa3-Cys-Xaa3-Asp-Ser-Cys-Arg-Xaa5-Leu-Cys-Cys-# (SEQ ID NO:232)

Name: T3.1
Species: tulipa
Cloned: Yes

DNA Sequence:
CGACCTCAAGAGGGATCGATAGCAGTTCATGTCTAAACTGGGAGTCTTGTTGACAA
TCTGTCTGCTTCTGTTTCCCCTTACTGCTCTGCCGATGGATGGAGATGAACCTGCAG
ACCGACCTGCAGAGCGTATGCAGGACAACATTTCATCTGAGCAGCATCCCTTGTTTG
AGGAGAGACACGGATGTTGCAAGGGGCCCGAAGGATGCTCCTCCAGAGAATGCAG
ACCCCAACATTGTTGCGGTCGACGATAACGTGTTGAGGGCCAACTTTGTTATCACGG
CTACGTCAAGTGTTTAGTGAATAAGTAAAATGATTGCAG (SEQ ID NO:233)

Translation:
MSKLGVLLTICLLLFPLTALPMDGDEPADRPAERMQDNISSEQHPLFEERHGCCKGPEGC
SSRECRPQHCCGRR (SEQ ID NO:234)

Toxin Sequence:
His-Gly-Cys-Cys-Lys-Gly-Xaa3-Xaa1-Gly-Cys-Ser-Ser-Arg-Xaa1-Cys-Arg-Xaa3-Gln-His-Cys-Cys-# (SEQ ID NO:235)

Name: Fi3.1
Species: figulinus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGCTGACCATCT
GTCTGCTTCTGATTCCCCTTACTGCTCTTTCGCTGGATGGAGATCAACCTGCAGACC
GACCTGCAGAGCGTATGCAGGATGGAATTTCATCTGAACAGCATCCCATGTTTGATC
CCGTCAGACGGTGTTGCCCGTGGCCATGCAACATAGGATGCGTACCTTGTTGTTGAT
GACCAGTTTTGTTATCGCGGCCTCATCAAATGTCTAATGAATAAGTAAAACGATTGC
AGT (SEQ ID NO:236)

Translation:
MMSKLGVLLTICLLLIPLTALSLDGDQPADRPAERMQDGISSEQHPMFDPVRRCCPWPC
NIGCVPCC (SEQ ID NO:237)

Toxin Sequence:
Cys-Cys-Xaa3-Xaa4-Xaa3-Cys-Asn-Ile-Gly-Cys-Val-Xaa3-Cys-Cys-^ (SEQ ID NO:238)

Name: Fi3.2
Species: figulinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTTTAAACTGGGAGTCCTGTTGACCATCTG
TATGCTTCTGTTTCCCTTTACTGCTCTTCCGCTGGATGGAGAGCAACCTGCAGACCA
ACCTGCAGAGCGCATGCAGTATGACATGTTACGTGCAATGAATCCCTGGTTTGATCC
CGTCAAAAGGTGCTGCTCGAAGAACTGCGCAGTATGCATCCCTTGTTGCCCGTAACT
GACCAGCTTGATTATCGCGGCCAAGGCTCTAATGAATAAGTAAAACGATTGCAGT
(SEQ ID NO:239)

Translation:
MMFKLGVLLTICMLLFPFTALPLDGEQPADQPAERMQYDMLRAMNPWFDPVKRCCSK
NCAVCIPCCP (SEQ ID NO:240)

Toxin Sequence:
Cys-Cys-Ser-Lys-Asn-Cys-Ala-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-^ (SEQ ID NO:241)

Name: Fi3.3
Species: figulinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGAGAGTCTTGTTGACCTTATG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCGCTGAATGAAGATCAACCTGCAGAGCGT
ATGCAGGACGACAATTCATCTGAGCAGCACCCCTTGTATGACCACAAACGAAAGTG
TTGCCGGTGGCCATGCCCCGCAAGATGCGGCTCTTGTTGCCTGTAATAACGTGTTGG
CCAACTTTGTTATCACGGCCACGTCAAATGTTTAATGAATAAGTAAAACGATTGCAG
T (SEQ ID NO:242)

Translation:
MMSKLRVLLTLCLLLFPLTALPLNEDQPAERMQDDNSSEQHPLYDHKRKCCRWPCPAR
CGSCCL (SEQ ID NO:243)

Toxin Sequence:
Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ala-Arg-Cys-Gly-Ser-Cys-Cys-Leu-^ (SEQ ID NO:244)

Name: Fi3.4
Species: figulinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCTTATG
TCTGCTTCTGTTTCCCCTGACTGCTCTTCCGCTGGATGAAGATCAAGCTGCAGACCG
ACCTGCAGAGCGTATGCAGGGCATGTCATCTGAACAGCATCCCTTCTTTGATCCCGT
CAAACGGTGTTGCGAGTTGTCACGCTGCCTTGGATGCGTCCCTTGTTGCACATCTTA
ATAACGTGTGGATGACCAACTGTGTTATCACGGCCACGTCAAGTGTCTAATGAATA
AGTAAAATGATTGCAGT (SEQ ID NO:245)

Translation:
MMSKLGVLLTLCLLLFPLTALPLDEDQAADRPAERMQGMSSEQHPFFDPVKRCCELSRC
LGCVPCCTS (SEQ ID NO:246)

Toxin Sequence:
Cys-Cys-Xaa1-Leu-Ser-Arg-Cys-Leu-Gly-Cys-Val-Xaa3-Cys-Cys-Thr-Ser-^ (SEQ ID NO:247)

Name: Fi3.5
Species: figulinus
Cloned: Yes

DNA Sequence:

CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCTTATG
TCTGCTTCTGTTTCCCCTGACTGCTCTTCCGCTGGATGAAGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGGCATGTCATCTGAACAGCATCCCTTCTTTGATCCCGT
CAAACGGTGTTGCGAGTTGTCAAAATGCCATGGATGCGTCCCTTGTTGCATACCTTA
ATAACGTGCGGATGACCAACTGTGTTATCACGGCCACGTCAAGTGTCTAATGAATA
AGTAAAATGATTGCAGT (SEQ ID NO:248)

Translation:
MMSKLGVLLTLCLLLFPLTALPLDEDQPADRPAERMQGMSSEQHPFFDPVKRCCELSKC
HGCVPCCIP (SEQ ID NO:249)

Toxin Sequence:
Cys-Cys-Xaa1-Leu-Ser-Lys-Cys-His-Gly-Cys-Val-Xaa3-Cys-Cys-Ile-Xaa3-^ (SEQ ID NO:250)

Name: Qc3.2
Species: quercinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTCGGAGTCTTGTTGACCATCTG
TCTGGTTCTGTTTCCCCTTACAGCTCTTCAGCTGGATGGAGATCAACCTGCAGACCG
ACCTGCAGAGCGTACGCAGGACATTTCATCTGAACAGTATCGAAAGTTTGATCAGA
GACAGAGGTGTTGCCGGTGGCCATGCCCCGGTAGTTGCAGATGCTGCCGTTATCGTT
AACGTGTTGGTGACCAGCTTTGTTATCACGACCACGCCAAGTGTCTAACGAATAAGT
AAAATGATTGCAGT (SEQ ID NO:251)

Translation:
MMSKLGVLLTICLVLFPLTALQLDGDQPADRPAERTQDISSEQYRKFDQRQRCCRWPCP
GSCRCCRYR (SEQ ID NO:252)

Toxin Sequence:
Xaa2-Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Gly-Ser-Cys-Arg-Cys-Cys-Arg-Xaa5-Arg-^
(SEQ ID NO:253)

Name: Qc3.3
Species: quercinus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCACTGGATGGAGATCAACCTGCAGATCAA
TCTGCAGAGCGACCTGCAGAGCGTACGCAGGACGACATTCAGCAGCATCCGTTATA
TGATCCGAAAAGAAGGTGTTGCCGTTATCCATGCCCCGACAGCTGCCACGGATCTTG
CTGCTATAAGTGATAACATGTTGATGGCCAGCTTTGTTATCACGGCCACGTCAAGTG
TCTAATGAATAAGTAAAACGATTGCAGT (SEQ ID NO:254)

Translation:
MMSKLGVLLTICLLLFPLTALPLDGDQPADQSAERPAERTQDDIQQHPLYDPKRRCCRY
PCPDSCHGSCCYK (SEQ ID NO:255)

Toxin Sequence:
Arg-Cys-Cys-Arg-Xaa5-Xaa3-Cys-Xaa3-Asp-Ser-Cys-His-Gly-Ser-Cys-Cys-Xaa5-Lys-^ (SEQ ID NO:256)

Name: Wi3.1
Species: wittigi
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCA
TTACTGCTCTTCCGGTGGGTGGAGATCAGCCTGCAGACCGACTTGCAGAGCGTATGC
AGGACGACACTTCATCTGAGCAGCATCCCTTTGAAAAGAGACTACCATCATGTTGC
GACTTTGAGAGGCTTTGCGTAGTACCAGCATGCATACGTCATCAGTGTTGCACAGGA
TAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:257)

Translation:
MMSKLGVLLTICLLLFPITALPVGGDQPADRLAERMQDDTSSEQHPFEKRLPSCCDFERL
CVVPACIRHQCCTG (SEQ ID NO:258)

Toxin Sequence:
Leu-Xaa3-Ser-Cys-Cys-Asp-Phe-Xaa1-Arg-Leu-Cys-Val-Val-Xaa3-Ala-Cys-Ile-Arg-His-Gln-Cys-Cys-Thr-# (SEQ ID NO:259)

Name: bt3a
Species: betulinus
Isolated: Yes

Toxin Sequence:

Cys-Cys-Lys-Gln-Ser-Cys-Thr-Thr-Cys-Met-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID NO:260)

Name: T3.2
Species: tulipa
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACAATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTGCCGATGGATGGAGATGAACCTGCAGACCGACCTGCAGAGCGTATG
CAGGACAACATTTCATCTGAGCAGCATCCCTTGTTTGAGGAGAGACACGGATGTTG

CGAGGGGCCGAAGGGATGCTCCTCCAGAGAATGCAGACCCCAACATTGTTGCGGTC
GACGATAACGTGTTGATGACCAACTNTCTCGAG (SEQ ID NO:261)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDEPADRPAERMQDNISSEQHPLFEERHGCCEGPK
GCSSRECRPQHCCGRR (SEQ ID NO:262)

Toxin Sequence:
His-Gly-Cys-Cys-Xaa1-Gly-Xaa3-Lys-Gly-Cys-Ser-Ser-Arg-Xaa1-Cys-Arg-Xaa3-Gln-His-Cys-Cys-# (SEQ ID NO:263)

Name: A3.5
Species: aurisiacus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTACTTCTGTTTCCCC
TTACTGCTTTTCCGATGGATGGAGATCAACCTGCAGACCAACCTGCAGATCGTATGC
AGGACGACATTTCATCTGAGCAGTATCCCTTGTTTGATAAGAGACAAAAGTGTTGCA
CTGGGAGGAAGGGGTCATGCTCCGGCAAAGCATGCAAAAATCTCAAATGTTGCTCT
GGACGATAACGTGTTGATGACCAACTTTCTCGAN (SEQ ID NO:264)

Translation:
MMSKLGVLLTICLLLFPLTAFPMDGDQPADQPADRMQDDISSEQYPLFDKRQKCCTGRK
GSCSGKACKNLKCCSGR (SEQ ID NO:265)

Toxin Sequence:
Xaa2-Lys-Cys-Cys-Thr-Gly-Arg-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Asn-Leu-Lys-Cys-Cys-Ser-# (SEQ ID NO:266)

Name: Bt3.5
Species: betulinus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTGTTCCGTTGGATGGAGATCAACCTGCAGACCAACCTGCAGAGCGTATGC
AGAACGAGCAGCATCCCTCGTTTGATCAGAAAAGAAGGTGCTGCCGGTGGCCATGC
CCCAGTATATGCGGCATGGCTAGGTGTTGCTTCGTCATGATAACGTGTTGATGACCA
ACTTTCTCGAG (SEQ ID NO:267)

Translation:
MMSKLGVLLTICLLLFPLTAVPLDGDQPADQPAERMQNEQHPSFDQKRRCCRWPCPSIC
GMARCCFVMITC (SEQ ID NO:268)

Toxin Sequence:

Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ser-Ile-Cys-Gly-Met-Ala-Arg-Cys-Cys-Phe-Val-Met-Ile-Thr-Cys-^ (SEQ ID NO:269)

Name: Bt3.6
Species: betulinus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGATCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTGTTCCGCTGGATGGAGATCAGCCTGCAGAGCGTACGCAGATCGAGCAG
CATCCCTTGTTTGACCAGAAAAGAAGGTGTTGCCGGTGGCCATGCCCCAGTAGATG
CGGCATGGCTAGGTGTTGCTTCGTCATGATAACGTGTTGATGANCGACCTCTCNAG
(SEQ ID NO:270)

Translation:
MMSKLGVLLIICLLLFPLTAVPLDGDQPAERTQIEQHPLFDQKRRCCRWPCPSRCGMAR
CCFVMITC (SEQ ID NO:271)

Toxin Sequence:
Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ser-Arg-Cys-Gly-Met-Ala-Arg-Cys-Cys-Phe-Val-Met-Ile-Thr-Cys-^ (SEQ ID NO:272)

Name: Pr3.1
Species: parius
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCGATGGATGGTGATCAACCTGCAGACCGACTTGTAGAGCGTATGC
AGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGAAAAGAGAAGAGGAGGCTGT
TGCACACCTCCGAAGAAATGCAAAGACCGAGCCTGCAAACCTGCACGTTGCTGCGG
CCCAGGATAACGTGTTGATGACCAACTTTCTCGCC (SEQ ID NO:273)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADRLVERMQDNISSEQHPFFEKRRGGCCTPP
KKCKDRACKPARCCGPG (SEQ ID NO:274)

Toxin Sequence:
Arg-Gly-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Lys-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:275)

Name: Pr3.2
Species: parius
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCGATGGATGGTGATCAACCTGCAGACCGACTTGTAGAGCGTATGC
AGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGAAAAGAGAAGAGGCTGTTGC
ACACCTCCGAGGAAATGCAAAGACCGAGCCTGCAAACCTGCACGTTGTTGCGGCCC
AGGATAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:276)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQPADRLVERMQDNISSEQHPFFEKRRGCCTPPR
KCKDRACKPARCCGPG (SEQ ID NO:277)

Toxin Sequence:
Arg-Gly-Cys-Cys-Thr-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:278)

Name: Ct3.1
Species: coronatus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCAA
TTACTGCCCTTCCGCTGGATGAAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
AGGACATTGCAACTGAACAGCATCCCTTGTTTGATCCCGTCAAACGGTGCTGCGATT
GGCCATGCATCCCAGGATGCACCCCTTGTTGCTTGCCTTGATAACGTGTTGATGACC
AACTTTCTCGAG (SEQ ID NO:279)

Translation:
MMSKLGVLLTICLLLFPITALPLDEDQPADRPAERMQDIATEQHPLFDPVKRCCDWPCIP
GCTPCCLP (SEQ ID NO:280)

Toxin Sequence:
Cys-Cys-Asp-Xaa4-Xaa3-Cys-Ile-Xaa3-Gly-Cys-Thr-Xaa3-Cys-Cys-Leu-Xaa3-^ (SEQ ID NO:281)

Name: Ms3.1
Species: musicus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCCTGTTGACCATCTGTCTGCTTCTGTTTCCTC
TTTCTGCTCTTCCGATGGATGAAGATCAACTTGCAGACCTACCTGCAGAGCGTATGC
GGGACACTGCAACTGTAGATCATCCCTCCTATGATCCTGACAAAGCGTGCTGCGAG
CAGAGCTGTACAACATGCTTTCCGTGCTGCTAGCCTTGAACACAGTAACGTGTTGAT
GACCAACTTTCTCGAG (SEQ ID NO:282)

Translation:
MMSKLGVLLTICLLLFPLSALPMDEDQLADLPAERMRDTATVDHPSYDPDKACCEQSCT TCFPCC (SEQ ID NO:283)

Toxin Sequence:
Ala-Cys-Cys-Xaa1-Gln-Ser-Cys-Thr-Thr-Cys-Phe-Xaa3-Cys-Cys-^ (SEQ ID NO:284)

Name: bt3b
Species: betulinus
Isolated: Yes

Toxin Sequence:

Ala-Cys-Cys-Xaa1-Gln-Ser-Cys-Thr-Thr-Cys-Met-Xaa3-Cys-Cys-^ (SEQ ID NO:285)

Name: bt3c
Species: betulinus
Isolated: Yes

Toxin Sequence:
Cys-Cys-Xaa1-Gln-Ser-Cys-Thr-Thr-Cys-Met-Xaa3-Cys-Cys-Xaa4-? (SEQ ID NO:286)

Name: Pn3.2
Species: pennaceus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC TTACTGCTCTTCCGCTGGATGGAGATCAACCTGCATACCAAGCTGCAGAGCGTATGC AGGCCGAGCATCATCCCTTGTTTGATCAGAAAAGACGGTGCTGCAAGTTTCCATGCC CCGATAGTTGCAAATATTTGTGTTGCGGGTGATGATAACATGTTGATGACCAACTTT CTTGAG (SEQ ID NO:287)

Translation:
MMSKLGVLLTICLLLFPLTALPLDGDQPAYQAAERMQAEHHPLFDQKRRCCKFPCPDSC KYLCCG (SEQ ID NO:288)

Toxin Sequence:
Arg-Cys-Cys-Lys-Phe-Xaa3-Cys-Xaa3-Asp-Ser-Cys-Lys-Xaa5-Leu-Cys-Cys-# (SEQ ID NO:289)

Name: Pu3.2
Species: pulicarius

Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCGATGGATGGTGATCAACTTGCAGACCGACTTGTAGAGCGTATGC
AGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGATCCCGTCAAACGGTGTTGCG
TCAGCTGTTACATGGGATGCATCCCTTGTTGCTTCTAGTAATAACGTGTTGATGACC
AACTTTCTCGAG (SEQ ID NO:290)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQLADRLVERMQDNISSEQHPFFDPVKRCCVSCY
MGCIPCCF (SEQ ID NO:291)

Toxin Sequence:
Cys-Cys-Val-Ser-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:292)

Name: Pu3.3
Species: pulicarius
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCGTCTGTCTGCTTCTGTGTCCCC
TTACTGCTCTTCCACTGGATGAAGATCAACTTGCAGACCGACCTGCAGAGCGTATGC
AGGATGACACTTCAGCTGCACAGATTTTCGGGTTTGATCCCGTCAAACGGTGCTGCA
AATTGCTATGCTACTCGGGATGCACTCCTTGTTGCCATATTTGATAACGTGTTGATG
ACCAACTTTCTCGAG (SEQ ID NO:293)

Translation:
MMSKLGVLLTVCLLLCPLTALPLDEDQLADRPAERMQDDTSAAQIFGFDPVKRCCKLLC
YSGCTPCCHI (SEQ ID NO:294)

Toxin Sequence:
Cys-Cys-Lys-Leu-Leu-Cys-Xaa5-Ser-Gly-Cys-Thr-Xaa3-Cys-Cys-His-Ile-^ (SEQ ID NO:295)

Name: Ra3.2
Species: rattus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTGTGTTTCCGC
TTACTGCTCTTCCGATGGATGGTGATCAACCTGCAGACCGACTTGTAGAGCGTATAC
AGGACAACATTTCATCTGAGCAGCATCCCTTCTTTGAAAAGAGAAGAGGCTGTTGC
GCACCTCCGAGGAAATGCAAAGACCGAGCCTGCAAACCTGCACGTTGCTGCGGCCC
AGGATAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:296)

Translation:

MMSKLGVLLTICLLVFPLTALPMDGDQPADRLVERIQDNISSEQHPFFEKRRGCCAPPRK
CKDRACKPARCCGPG (SEQ ID NO:297)

Toxin Sequence:
Arg-Gly-Cys-Cys-Ala-Xaa3-Xaa3-Arg-Lys-Cys-Lys-Asp-Arg-Ala-Cys-Lys-Xaa3-Ala-Arg-Cys-Cys-Gly-Xaa3-# (SEQ ID NO:298)

Name: Sm3.3
Species: stercusmuscarum
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACAATCTGTCTGCTTCTGTTTCCCC
TTATTGCTCTTCCGCTGGATGGAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
AGGACGACATTTCATCTGAGAAGCATCCCTTGTTTGATAAGAGACAACGGTGTTGC
AATGGGCGGAGGGGATGCTCCAGCAGATGGTGCAGAGATCACTCACGTTGTTGCGG
TCGACGATAACGTGTTGATGACCAACTTTCTCGAG (SEQ ID NO:299)

Translation:
MMSKLGVLLTICLLLFPLIALPLDGDQPADRPAERMQDDISSEKHPLFDKRQRCCNGRRG
CSSRWCRDHSRCCGRR (SEQ ID NO:300)

Toxin Sequence:
Xaa2-Arg-Cys-Cys-Asn-Gly-Arg-Arg-Gly-Cys-Ser-Ser-Arg-Xaa4-Cys-Arg-Asp-His-Ser-Arg-Cys-Cys-# (SEQ ID NO:301)

Name: Eb3.1
Species: ebraeus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCACTGGATGAAGGTCAACCTGCAGACCTACCTGCAGAGCGTATGC
AGGACATTGCAACTGAACAGCATCCCTTGTTTGATCCTGTCAAACGGTGTTGCGAGC
AGCCATGCTACATGGGATGCATCCCTTGTTGCTTCTAATAATAACGTGTTGATGACC
AACTTTCTCGAG (SEQ ID NO:302)

Translation:
MMSKLGVLLTICLLLFPLTALPLDEGQPADLPAERMQDIATEQHPLFDPVKRCCEQPCY
MGCIPCCF (SEQ ID NO:303)

Toxin Sequence:
Cys-Cys-Xaa1-Gln-Xaa3-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:304)

Name: Eb3.2
Species: ebraeus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTCTTCCACTGGATGAAGATCAACCTGCAGACCTACCTGCAGAGCGTATGC
AGGACATTGCAACTGAACAGCATCCCTTGTTTGATCCTGTCAAACGGTGCTGCGCGC
AGCCATGCTACATGGGATGCATCCCTTGTTGCTTCTAATAATAACGTGTTGATGACC
AACTTTCTCGAG (SEQ ID NO:305)

Translation:
MMSKLGVLLTICLLLFPLTALPLDEDQPADLPAERMQDIATEQHPLFDPVKRCCAQPCY
MGCIPCCF (SEQ ID NO:306)

Toxin Sequence:
Cys-Cys-Ala-Gln-Xaa3-Cys-Xaa5-Met-Gly-Cys-Ile-Xaa3-Cys-Cys-Phe-^ (SEQ ID NO:307)

Name: Fd3.2
Species: flavidus
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCCC
TTACTGCTGTTCCGTTGGATGGAGATCAACCTGCAGACCAGCCTGCAGAGCGTATGC
AGAACGAGCAGCATCCCTTGTTTGATCAGAAAAGAAGGTGCTGCCGGTGGCCATGC
CCCAGTATATGCGGCATGGCTAGGTGTTGCTCGTCATGATAACGTGTTGATGACCAA
CTTTCTCGAG (SEQ ID NO:308)

Translation:
MMSKLGVLLTICLLLFPLTAVPLDGDQPADQPAERMQNEQHPLFDQKRRCCRWPCPSIC
GMARCCSS (SEQ ID NO:309)

Toxin Sequence:
Arg-Cys-Cys-Arg-Xaa4-Xaa3-Cys-Xaa3-Ser-Ile-Cys-Gly-Met-Ala-Arg-Cys-Cys-Ser-Ser-^
(SEQ ID NO:310)

Name: Mf3.1
Species: miliaris
Cloned: Yes

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTGTCTGCTTCTGTTTCCAA
TTACTGCCCTTCCACTGGATGAAGATCAACCTGCAGACCGACCTGCAGAGCGTATGC
AGGACATTGCAACTGAACAGCATCCCTTGTTTGATCCCGTCAAACGGTGTTGCGATT

GGCCATGCAGCGCAGGATGCTACCCTTGTTGCTTCCCTTAATAACGTGTTGATGACC
AACTNANGNAAAAAAA (SEQ ID NO:311)

Translation:
MMSKLGVLLTICLLLFPITALPLDEDQPADRPAERMQDIATEQHPLFDPVKRCCDWPCSA
GCYPCCFP (SEQ ID NO:312)

Toxin Sequence:
Cys-Cys-Asp-Xaa4-Xaa3-Cys-Ser-Ala-Gly-Cys-Xaa5-Xaa3-Cys-Cys-Phe-Xaa3-^ (SEQ ID NO:313)

Name: Mf3.2
Species: miliaris
Cloned: Yes
Notes:

DNA Sequence:
GGATCCATGATGTCTAAACTGGGAGTGGTGCCATTCGTCTTTCTGGTCCTGTTTCCCC
TGGCAACACTCCAACTGGATGCAGATCAACCTGCAGACCGACCTGCGCGTAAAAAG
GGCATTGCAACTAAACGGCATCCCTTGTCTGATCCTGTCAGAGGGTGTTGCCCTCCA
ATGTGCACACCATGCTTCCCTTGCTGTTTTCGTTAATAACGTGTTGATGNATGATGN
AN (SEQ ID NO:314)

Translation:
MMSKLGVVPFVFLVLFPLATLQLDADQPADRPARKKGIATKRHPLSDPVRGCCPPMCTPCFPCC
FR (SEQ ID NO:315)

Toxin Sequence:
Gly-Cys-Cys-Xaa3-Xaa3-Met-Cys-Thr-Xaa3-Cys-Phe-Xaa3-Cys-Cys-Phe-Arg-^ (SEQ ID NO:316)

Name: Af3.1
Species: ammiralis
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTACTGCTCTTCCGCTGGATGGAGATCAACCTGCAGACCA
AGCTGCAGAGCGTATGCAGGCCGAGCAGCATCCCTTGTTTGATCAGAAAAGACGGT
GTTGCAGGTTTCCATGCCCCGATACTTGCAGACATTTGTGTTGCGGGTGATGATAAC
GTGCTGATGACCCACTTTGTCATCACGGCTACGTCAAGTGTCTAATGAATAAGTAAA
ATGATTGCAGT (SEQ ID NO:317)

Translation:
MMSKLGVLLTICLLLFPLTALPLDGDQPADQAAERMQAEQHPLFDQKRRCCRFPCPDTC
RHLCCG (SEQ ID NO:318)

Toxin Sequence:
Arg-Cys-Cys-Arg-Phe-Xaa3-Cys-Xaa3-Asp-Thr-Cys-Arg-His-Leu-Cys-Cys-# (SEQ ID NO:319)

Name: Af3.2
Species: ammiralis
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTTTAAACTGGGAGTCTTGCTGACCATCTG
TCTACTTCTGTTTTCCCTTAATGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCA
ACCTGCAGAGCGTCTGCTGGACGACATTTCATCTGAAAATAATCCCTTTTATGATCC
CGCCAAACGGTGTTGCATGACTTGCTTCGGTTGCACACCTTGTTGTGGATGACCAGC
CTCATCAAGTGTCTAACGAATAAGTAAAACGATTGCAGT (SEQ ID NO:320)

Translation:
MMFKLGVLLTICLLLFSLNAVPLDGDQPADQPAERLLDDISSENNPFYDPAKRCCMTCF
GCTPCCG (SEQ ID NO:321)

Toxin Sequence:
Cys-Cys-Met-Thr-Cys-Phe-Gly-Cys-Thr-Xaa3-Cys-Cys-# (SEQ ID NO:322)

Name: Af3.3
Species: ammiralis
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCAGGACCGCCTTCCAACTGAAAATCATCCCTTATATGATC
CCGTCAAACGGTGTTGCGATGATTCGGAATGCGACTATTCTTGCTGGCCTTGCTGTA
TTTTTTCATAACCTTTGTTATCGCGGCCTCATCCTAGTGTCAAATGAATAAGTAAAA
CGATTGCAGT (SEQ ID NO:323)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCIFS (SEQ ID NO:324)

Toxin Sequence:
Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Ile-Phe-Ser-^ (SEQ ID NO:325)

Name: Af3.4
Species: ammiralis
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTTTAAACTCGGAGTCTTGCTGACCATCTG
TCTACTTCTGTTTTCCCTAATtGCTGTTCCGCTGGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGACCGCCTTCCAACTGAAAATCATCCCTTATATGATCCC
GTCAAACGGTGTTGCAGGTTGTTATGCCTCAGTTGCAACCCTTGTTGTGGATGACCA
GCTTTGTTATCACGGCCTCATCAAGTGTCTAATGAATAAGTAAAACGATTGCAGT
(SEQ ID NO:326)

Translation:
MMFKLGVLLTICLLLFSLIAVPLDGDQHADQPAERLQDRLPTENHPLYDPVKRCCRLLCL
SCNPCCG (SEQ ID NO:327)

Toxin Sequence:
Cys-Cys-Arg-Leu-Leu-Cys-Leu-Ser-Cys-Asn-Xaa3-Cys-Cys-# (SEQ ID NO:328)

Name: Af3.6
Species: ammiralis
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCAGGACCGCATTCCAACTGAAGATCATCCCTTATTTGATC
CCAACAAACGGTGTTGCGATGATTCGGAATGCGGCTATTCATGCTGGCCTTGCTGTT
ATGGATAAGCTTTGTTATCGCGGCCTCATCCAGTGTCAACGAATAAGTAAAACGATT
GCAGT (SEQ ID NO:329)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRIPTEDHPLFDPNKRCCDDSEC
GYSCWPCCYG (SEQ ID NO:330)

Toxin Sequence:
Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Gly-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa5-# (SEQ ID NO:331)

Name: Sf3.1
Species: spurius
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGCTGACCATCT
GTCTGCTTCTGTTTCCACGTACTTCTCTTCCGCTGGATGGAGATCAACCTGCAGTCCG
ATCTGCAAAGCGTATGCATTCATCTATACAGCGTCGTTTCTTTGATCCCGTCAAACG
GTGTTGCCCTAGATGCAGCGAGTGCAACCCTTGTTGTGGATGACCAGCTTTGTCATC
GCGGCCTCATTAAGTGTCTAATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:332)

Translation:
MMSKLGVLLTICLLLFPRTSLPLDGDQPAVRSAKRMHSSIQRRFFDPVKRCCPRCSECNP CCG (SEQ ID NO:333)

Toxin Sequence:
Cys-Cys-Xaa3-Arg-Cys-Ser-Xaa1-Cys-Asn-Xaa3-Cys-Cys-# (SEQ ID NO:334)

Name: Om3.1
Species: omaria
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTCGTTGACCATCT GTCTACTTCTATTTTCCCTTACTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCA ACCTGCAGAGCGTCTGCAGGGCGACATTTTATCTGAAAAGCATCCCTTATTTAATCC CGTCAAACGGTGTTGCGATGAGGAAGAATGCAGCAGTGCATGCTGGCCTTGTTGTT GGGGGTGATCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAAT GATTGCAGT (SEQ ID NO:335)

Translation:
MMSKLGVSLTICLLLFSLTAVPLDGDQHADQPAERLQGDILSEKHPLFNPVKRCCDEEEC SSACWPCCWG (SEQ ID NO:336)

Toxin Sequence:
Cys-Cys-Asp-Xaa1-Xaa1-Xaa1-Cys-Ser-Ser-Ala-Cys-Xaa4-Xaa3-Cys-Cys-Xaa4-# (SEQ ID NO:337)

Name: Om3.2
Species: omaria
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGATCATCTG TCTACTTCTGTGTCCCCTTACTGCTGTTCTGGAGGATGGAGATCAACCTGCAGACCG ACCTGCAGAGCGTATGCAGGACGACATTTCAACTGAGCATCATCCCTTTTATGATCC CGTCAAACGGTGTTGCAAGTACGGGTGGACATGCTTGCTAGGATGCACTCCTTGTGA TTGTTGACCAGTTTTGTTATCGCGGCCTCGTCAAGTGTCTAATGAATAAGTAAAACG ATTGCAGT (SEQ ID NO:338)

Translation:
MMSKLGVLLIICLLLCPLTAVLEDGDQPADRPAERMQDDISTEHHPFYDPVKRCCKYGW TCLLGCTPCDC (SEQ ID NO:339)

Toxin Sequence:

Cys-Cys-Lys-Xaa5-Gly-Xaa4-Thr-Cys-Leu-Leu-Gly-Cys-Thr-Xaa3-Cys-Asp-Cys-^ (SEQ ID NO:340)

Name: Om3.3
Species: omaria
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTATACTGGGAGTCTTGTTGATCATCTG
TCTACTTCTGTGTCCCCTTACTGCTGTTCTGGAGGATGGAGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGACGGCATTTCATCTGAACATCATCCCTTTTTGGATCC
CGTCAAACGGTGTTGCCATCTATTGGCATGCCGCTTTGGATGCTCGCCTTGTTGTTG
GTGACCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAACGATT
GCAGT (SEQ ID NO:341)

Translation:
MMSILGVLLIICLLLCPLTAVLEDGDQPADRPAERMQDGISSEHHPFLDPVKRCCHLLAC
RFGCSPCCW (SEQ ID NO:342)

Toxin Sequence:
Cys-Cys-His-Leu-Leu-Ala-Cys-Arg-Phe-Gly-Cys-Ser-Xaa3-Cys-Cys-Xaa4-^ (SEQ ID NO:343)

Name: Om3.4
Species: omaria
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGATCATCTG
TCTACTTCTTTGTCCCCTTACTGCTGTTCCGCAGGATGGAGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGGCGGCATTTCATCTGAACATCATCCCTTTTTTGATCC
CGTCAAACGGTGTTGCAGGTACGGGTGGACATGCTGGCTAGGATGCACTCCCTGTG
GTTGTTGACCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAAC
GATTGCAGT (SEQ ID NO:344)

Translation:
MMSKLGVLLIICLLLCPLTAVPQDGDQPADRPAERMQGGISSEHHPFFDPVKRCCRYGW
TCWLGCTPCGC (SEQ ID NO:345)

Toxin Sequence:
Cys-Cys-Arg-Xaa5-Gly-Xaa4-Thr-Cys-Xaa4-Leu-Gly-Cys-Thr-Xaa3-Cys-Gly-Cys-^ (SEQ ID NO:346)

Name: Ep3.1
Species: episcopatus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTACTTCTGTTTTCCCTTATTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTTTATCTGAAAAGCATCCCTTATTTATGCCT
GTCAAACGGTGTTGCGATGAGGACGAATGCAACAGTTCATGCTGGCCTTGTTGTTGG
GGGTGATCAGCTTTGTTATCGCGGCCTGATCAAGTGTATAATGAATAAGTAAAACG
ATTGCAGT (SEQ ID NO:347)

Translation:
MMSKLGVLLTICLLLFSLIAVPLDGDQHADQPAERLQGDILSEKHPLFMPVKRCCDEDEC
NSSCWPCCWG (SEQ ID NO:348)

Toxin Sequence:
Cys-Cys-Asp-Xaa1-Asp-Xaa1-Cys-Asn-Ser-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa4-# (SEQ ID NO:349)

Name: Ep3.2
Species: episcopatus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTACTTCTGTTTTCCCTTATTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTTTATCTGAAAAGCATCCCTTATTTATGCCT
GTCAAACGGTGTTGCGATGAGGACGAATGCAGCAGTTCATGCTGGCCTTGTTGTTGG
GGATGAGCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAACG
ATTGCAGT (SEQ ID NO:350)

Translation:
MMSKLGVLLTICLLLFSLIAVPLDGDQHADQPAERLQGDILSEKHPLFMPVKRCCDEDEC
SSSCWPCCWG (SEQ ID NO:351)

Toxin Sequence:
Cys-Cys-Asp-Xaa1-Asp-Xaa1-Cys-Ser-Ser-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa4-# (SEQ ID NO:352)

Name: Ep3.3
Species: episcopatus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTACTTCTGTTTTCCCTTACTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTTTATCTGAAAAGCATCCCTTATTTAATCCC
GTCAAACGGTGTTGCCCGGCGGCGGCATGTGCCATGGGATGCAAGCCTTGTTGTGG

ATGAGCAGCTTTGTTATCGTGGCCTCATCAAGTGTCTAATGAATAAGTAAAACGATT
GCAGT (SEQ ID NO:353)

Translation:
MMSKLGVLLTICLLLFSLTAVPLDGDQHADQPAERLQGDILSEKHPLFNPVKRCCPAAA
CAMGCKPCCG (SEQ ID NO:354)

Toxin Sequence:
Cys-Cys-Xaa3-Ala-Ala-Ala-Cys-Ala-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-# (SEQ ID NO:355)

Name: Au3.2
Species: aulicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTTCCGTTACTGCTCTTCCGCCGGATGGAGATCAACCTGCAGACCG
AGCTGCAGAGCGTAGGCAGGTCGAGCAGCATCCCGTGTTTGATCATGAAAGAGGGT
GTTGCTCGCCACCATGCCACAGTATTTGCGCTGCTTTCTGTTGCGGGTGATGATAAC
GTGTTGATGACCCACTTTGTCATCACGGCTGCGTCAAGTGTCTAATGAATAAGTAAA
ATGATTGCAGT (SEQ ID NO:356)

Translation:
MMSKLGVLLTICLLLFSVTALPPDGDQPADRAAERRQVEQHPVFDHERGCCSPPCHSIC
AAFCCG (SEQ ID NO:357)

Toxin Sequence:
Gly-Cys-Cys-Ser-Xaa3-Xaa3-Cys-His-Ser-Ile-Cys-Ala-Ala-Phe-Cys-Cys-# (SEQ ID NO:358)

Name: Au3.3
Species: aulicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTACTTCTGTTTTCCCTTACTGCTGTTCCGCTTGATGGAGATCAACATGCAGACCAA
CCTGCAGAGCGTCTGCAGGGCGACATTTTATCTGAAAAGCATCCCTTATTTAATCCC
GTCAAACGGTGTTGCCGACCGGTGGCATGTGCCATGGGATGCAAGCCTTGTTGTGG
ATGAGCAGCTTTGTTATCGTGGCCTCATCAAGTGTCTAATGAATAAGTAAAATGATT
GCAGT (SEQ ID NO:359)

Translation:
MMSKLGVLLTICLLLFSLTAVPLDGDQHADQPAERLQGDILSEKHPLFNPVKRCCRPVA
CAMGCKPCCG (SEQ ID NO:360)

Toxin Sequence:

Cys-Cys-Arg-Xaa3-Val-Ala-Cys-Ala-Met-Gly-Cys-Lys-Xaa3-Cys-Cys-# (SEQ ID NO:361)

Name: Au3.4
Species: aulicus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCaTGATGTCTAAACTGGGAGTCTTGTTGATCATCTG
TCTACTTCTGTCTCCCCTTACTGCTGTTCCGCTGGATGGAGATCAACCTGCAGACCG
ACCTGCAGAGCGTATGCAGGACGACATTTCATCTGAACATCAACCCATGTTTGATGC
CATCAGACAGTGTTGCCCGGCGGTGGCATGCGCCATGGGATGCGAGCCTTGTTGTG
GATGACCAGCTTTGTTATCGCGGCCTCATCAAGTGTCTAATGAATAAGTAAAATGAT
TGCAGT (SEQ ID NO:362)

Translation:
MMSKLGVLLIICLLLSPLTAVPLDGDQPADRPAERMQDDISSEHQPMFDAIRQCCPAVAC
AMGCEPCCG (SEQ ID NO:363)

Toxin Sequence:
Xaa2-Cys-Cys-Xaa3-Ala-Val-Ala-Cys-Ala-Met-Gly-Cys-Xaa1-Xaa3-Cys-Cys-# (SEQ ID NO:364)

Name: Ae3.1
Species: aureus
Cloned: Yes

DNA Sequence:
CAAGAAGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTTACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACATGCAGAGCGTCTGCATGACCGCCTTCCAACTGAAAATCATCCCTTATATGATC
CCGTCAAACGGTGTTGCGATGATTCGGAATGCGACTATTCTTGCTGGCCTTGCTGTA
TTTTTGGATAACCTTTGTTATCGCGGCCTCATCAAGTGTCAAATGAATAAGTAAAAC
GATTGCAGT (SEQ ID NO:365)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQHAERLHDRLPTENHPLYDPVKRCCDDSE
CDYSCWPCCIFG (SEQ ID NO:366)

Toxin Sequence:
Cys-Cys-Asp-Asp-Ser-Xaa1-Cys-Asp-Xaa5-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Ile-Phe-# (SEQ ID NO:367)

Name: Ae3.2
Species: aureus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGCCTTGTTGACCATCT
GTCTACTTCTGTTTTCCCTAACTGCTGTTCCGCTGGATGGAGATCAACATGCAGACC
AACCTGCAGAGCGTCTGCAGGACCGCATTCCAACTGAAAATCATCCCTTATTTGATC
CGAACAAACGGTGTTGCAATGATTGGGAATGCGACGATTCATGCTGGCCTTGCTGTT
ATGGATAACCTTTGTTATCGCGGCCTCATCAAGTGTCAAATGAATAAGTAAAACGAT
TGCAGT (SEQ ID NO:368)

Translation:
MMSKLGALLTICLLLFSLTAVPLDGDQHADQPAERLQDRIPTENHPLFDPNKRCCNDWE
CDDSCWPCCYG (SEQ ID NO:369)

Toxin Sequence:
Cys-Cys-Asn-Asp-Xaa4-Xaa1-Cys-Asp-Asp-Ser-Cys-Xaa4-Xaa3-Cys-Cys-Xaa5-# (SEQ ID NO:370)

Name: Cn3.1
Species: consors
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TTTGCTTCTGTTTCCCCTTACTGCTCTTCCAATGGATGGAGATCAATCTGTAGACCGA
CCTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCTGCATCCCTTGTTCAATCAG
AAAAGAATGTGTTGCGGCGAAGGTGCGCCATGCCCCAGCTATTTCAGAAACAGTCA
GATTTGTCATTGTTGTTAAATGACAACGTGTCGATGACCAACTTCGTTATCACGACT
AATGAATAAGTAAAATGATTGCAGT (SEQ ID NO:371)

Translation:
MMSKLGVLLTICLLLFPLTALPMDGDQSVDRPAERMQDDISSELHPLFNQKRMCCGEGA
PCPSYFRNSQICHCC (SEQ ID NO:372)

Toxin Sequence:
Met-Cys-Cys-Gly-Xaa1-Gly-Ala-Xaa3-Cys-Xaa3-Ser-Xaa5-Phe-Arg-Asn-Ser-Gln-Ile-Cys-His-Cys-Cys-^ (SEQ ID NO:373)

Name: Cn3.3
Species: consors
Cloned: Yes

DNA Sequence:
TAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACCATCTG
TCTGCTTCTGTTTCCCCTTATTGCTCTTCCAATGGATGGAGATCAACCTGCAGACCGA
CCTGCAGAGCGTATGCAgGACGACATTTCATCTCAGCAGCATCCCTTGTTTGATAAG
AGAGGCCGCTGTTGCGATGTGCCGAACGCATGCTCCGGCAGATGGTGCAGAGATCA

CGCACAATGTTGCGGATGACGATAACGTGTTGATGACCAACTTTGTGATCACGGCTA
CATCAAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:374)

Translation:
MMSKLGVLLTICLLLFPLIALPMDGDQPADRPAERMQDDISSQQHPLFDKRGRCCDVPN
ACSGRWCRDHAQCCG (SEQ ID NO:375)

Toxin Sequence:
Gly-Arg-Cys-Cys-Asp-Val-Xaa3-Asn-Ala-Cys-Ser-Gly-Arg-Xaa4-Cys-Arg-Asp-His-Ala-Gln-Cys-Cys-# (SEQ ID NO:376)

Name: Cn3.4
Species: consors
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGTTGACTGTCTG
TTTGCTTCTGTTTCCCCTTACTGCTCTTCCGATGGATGGAGATCAACCTGCAGACCAA
CCTGCAGAGCGTATGCAGGACGACATTTCATCTGAGCAGCATCCCTTGTTTGATAAG
AGACAAAGGTGTTGCACTGGGAAGAAGGGGTCATGCTCCGGTAAAGCATGCAAAA
GTCTCAAATGTTGCTCTGGACGATAACGTGTTGATGACCAACTTTGTTATCACGGCT
ACGTCAAGTGTCTAGTGAATAAGTAAAACGATTGCAGT (SEQ ID NO:377)

Translation:
MMSKLGVLLTVCLLLFPLTALPMDGDQPADQPAERMQDDISSEQHPLFDKRQRCCTGK
KGSCSGKACKSLKCCSGR (SEQ ID NO:378)

Toxin Sequence:
Xaa2-Arg-Cys-Cys-Thr-Gly-Lys-Lys-Gly-Ser-Cys-Ser-Gly-Lys-Ala-Cys-Lys-Ser-Leu-Lys-Cys-Cys-Ser-# (SEQ ID NO:379)

Name: Em3.1
Species: emaciatus
Cloned: Yes

DNA Sequence:
CAAGAGGGATCGATAGCAGTTCATGATGTCTAAACTGGGAGTCTTGCTGACCATCTGTCTGCTTCTGTT
TCCCCTTACTGTTCTTCCGATGGATGGAGATCAACCTGCAGACCTACCTGCATTGCGTGCGCAGTTCTT
TGCACCTGAACATAGTCCCCGGTTTGACCCCGTCAAACGGTGCTGCTCGCGGGATTGCAGTGTTTGCA
TCCCTTGTTGCCCGTATGGATCACCTTGATTATTGCGGCCACGTCAAGTGTCTAATGAATAAGTAAAAT
GATTGCAGT (SEQ ID NO:380)

Translation:
MMSKLGVLLTICLLLFPLTVLPMDGDQPADLPALRAQFFAPEHSPRFDPVKRCCSRDCSVCIPCCPYGSP
(SEQ ID NO:381)

Toxin Sequence:

Cys-Cys-Ser-Arg-Asp-Cys-Ser-Val-Cys-Ile-Xaa3-Cys-Cys-Xaa3-Xaa5-Gly-Ser-Xaa3-^ (SEQ ID NO:382)

Where:
Xaa1 is Glu or γ-carboxy-Glu
Xaa2 is Gln or pyro-Glu
Xaa3 is Pro or hydroxy-Pro
Xaa4 is Trp or bromo-Trp
Xaa5 is Tyr, ^{125}I-Tyr, mono-iodo-Tyr, di-iodo-Tyr, O-sulpho-Tyr or O-phospho-Tyr
^ is free carboxyl or amidated C-terminus, preferably free carboxyl
# is free carboxyl or amidated C-terminus, preferably amidated
? = Status of C-term not known.

TABLE2

Alignment of μ-Conopeptides (SEQ ID NO:)

TYPE 1

A3.4 (F283)	---CCKVQ-CES--C---TPCC^ (383)
Ak3.1 (F585)	---CCELP-CGPGFC---VPCC^ (384)
Ar3.1	---CCERP-CNIG-C---VPCC^ (385)
Bn3.1 (F586)	---CCNWP-CSMG-C---IPCCYY^ (386)
Bt3.1	---CCELP-CH-G-C---VPCCWP^ (387)
Bt3.2	---CCGLP-CN-G-C---VPCCWPS^ (388)
Bt3.3	---CCSRN-CAV--C---IPCCPNWPA^ (389)
bt3a	---CCKQS-CTT--C---MPCCW^ (390)
bt3b	--ACCXQS-CTT--C---MPCC^ (391)
bt3c	---CCEQS-CTT--C---MPCCW? (392)
Ca3.3	R--CCRYP-CPDS-C--HGSCCYK^ (393)
Ca3.4	---CCPPVACNMG-C---KPCC# (394)
Ca3.5	---CCDDSECDYS-C---WPCCMF# (395)
Ca3.6 (F349)	---CCRR--CYMG-C---IPCCF^ (396)
Circling	---CCPPVACNMG-C---KPCCG^ (397)
Comatose/Death	SKQCCHLAACRFG-C---TOCCN^ (398)
Cp3.1 (F594)	S--CCR--DCGED-C---VGCCR^ (399)
Ct3.1 (Z726)	---CCDWP-CIPG-C---TPCCLP^ (400)
Da3.1	---CCDDSECDYS-C---WPCCILS^ (401)
Da3.2	Z-QCCPPVACNMG-C---EPCC# (402)
Da3.3	---CCNAGFCRFG-C---TPCCW^ (403)
Di3.1	Z--CCVHP-C-P--C---TPCCR^ (404)
Fi3.1	---CCPWP-CNIG-C---VPCC^ (405)
Fi3.2	---CCSKN-CAV--C---IPCCP^ (406)
Fi3.3	---CCRWP-CP-ARC---GSCCL^ (407)
Fi3.4	---CCELSRCL-G-C---VPCCTS^ (408)
Fi3.5	---CCELSKCH-G-C---VPCCIP^ (409)

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Ge3.1 (F590)          Z--CCTF--CNFG-C---QPCCVP^ (410)
Ge3.2 (F343/Z734)     Z--CCTF--CNFG-C---QPCCLT^ (411)
Ge3.3 (F590           Z--CCTF--CNFG-C---QPCCVP^ (412)
Gm3.1                 ---CCDDSECDYS-C---WPCCMF# (413)
Gm3.2                 G--CCHLLACRFG-C---SPCCW^ (414)
Gm3.3                 ---CCSWDVCDHPSC---T-CCG# (415)
La3.1                 ---CCDWP-CS-G-C---IPCC^ (416)
Lp3.1 (F340)          ZINCCPWP-CPST-C--RHQCCH^ (417)
Lv3.1 (F341)          ZINCCPWP-CPDS-C--HYQCCH^ (418)
Mr3.2                 ---CCRLS-CGLG-C---HPCC# (419)
Mr3.3                 --ECCGSFACRFG-C---VPCCV^ (420)
Mr3.4                 SKQCCHLPACRFG-C---TPCCW^ (421)
Mr3.5 (F286)          -MGCCPFP-CKTS-C--TTLCC# (422)
Ms3.1 (Z738)          --ACCEQS-CTT--C---FPCC^ (423)
Nb3.1 (F87)           ---CCELP-CGPGFC---VPCC^ (424)
Pu3.1 (F339)          ---CCN-S-CYMG-C---IPCCF^ (425)
Qc3.1 (F342)          ZR-CCQWP-CPGS-C----RCCRT# (426)
Qc3.2                 ZR-CCRWP-CPGS-C----RCCRYR^ (427)
Qc3.3                 R--CCRYP-CPDS-C--HGSCCYK^ (428)
QcIIIA                ---CCSQD-CLV--C---IOCCPN# (429)
QcIIIB                ---CCSRH-CWV--C---IOCCPN? (430)
Ra3.1 (F351)          Z-TCCS-N-CGED-C---DGCCQ^ (431)
Scratcher I           ---CCR-T-C-FG-C---TOCC# (433)
Ts3.1 (F592)          ---CCH-K-CYMG-C---IPCCI^ (434)
Ts3.2 (F345)          K--CCRPP-CAMS-C-GMARCCY^ (435)
Bt3.5 (Z495)          R--CCRWP-CPSI-C-GMARCCFVMITC^ (436)
Bt3.6 (Z497)          R--CCRWP-CP-SRC-GMARCCFVMITC^ (437)
Tx3.1                 F--CCDSNWCHISDC----ECCY# (438)
U014                  ---CCHWNWCDHL-C----SCCGS^ (439)
U017                  --DCCOLPACPFG-C---NOCC# (440)
U019                  ---CCAPSACRLG-C---ROCCR^ (441)
U020                  ---CCAOSACRLG-C---ROCCR^ (442)
U022                  ---CCAPSACRLG-C---RPCCR^ (443)
U024                  --GCCGSFACRFG-C---VOCCV^ (444)
U031                  ---CCSWDVCDHPSC----TCC# (445)
U032 (F353)           R--CCKFP-CPDS-C--RYLCC# (446)
Ae3.1                 ---CCDDSECDYS-C---WPCCIF# (447)
Ae3.2                 ---CCNDWECDDS-C---WPCCY# (448)
Af3.1                 R--CCR-FPCPDT-C---RHLCC# (449)
Af3.2                 ---CC--MTC-FG-C---TPCC# (450)
Af3.3                 ---CCDDSECDYS-C---WPCCIFS^ (451)
Af3.4                 ---CCR-LLC-LS-C---NPCC# (452)
Af3.6                 ---CCDDSECGYS-C---WPCCY# (453)
Au3.2                 G--CCS-PPCHSI-C--AAFCC# (454)
Au3.3                 ---CCRPVACAMG-C---KPCC# (455)
Au3.4                 Z--CCPAVACAMG-C---EPCC# (456)
Em3.1                 ---CCS-RDC-SV-C---IPCCPYGSP^ (457)
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Ep3.1                  ---CCDEDECNSS-C---WPCCW# (458)
Ep3.2                  ---CCDEDECSSS-C---WPCCW# (459)
Ep3.3                  ---CCPAAACAMG-C---KPCC# (460)
Om3.1                  ---CCDEEECSSA-C---WPCCW# (461)
Om3.3                  ---CCHLLACRFG-C---SPCCW^ (462)
Sf3.1                  ---CC--PRC-SE-C---NPCC# (463)
```

TYPE 2

```
Pn3.2 (AA049)          -RCC--KFP-CPDS-C--KYLCC# (464)
Fd3.2 (Z831)           -RCC--RWP-CPSI-C-GMARCCSS^ (465)
Pu3.3 (AA405)          --CC--KLL-CYSG-C---TPCCHI^ (466)
Eb3.1 (Z821)           --CC--EQP-CYMG-C---IPCCF^ (467)
Eb3.2 (Z822)           --CC--AQP-CYMG-C---IPCCF^ (468)
Pu3.2 (AA403)          --CC--V-S-CYMG-C---IPCCF^ (469)
Mf3.1 (Z882)           --CC--DWP-CSAG-C---YPCCFP^ (470)
Mf3.2 (Z885)           -GCC--PPM-C-TP-C---FPCCFR^ (471)
Ra3.2 (AA414)          RGCCAPPRK-CKDRACK-PARCCGP# (472)
Sm3.3 (AA419)          ZRCCNGRRG-CSSRWCRDHSRCC# (473)
Cn3.3                  GRCCDVPNA-CSGRWCRDHAQCC# (474)
Cn3.4                  ZRCCTGKKGSCSGKACKSL-KCCS# (475)
```

TYPE 3

```
A3.1                   -MCCGEGRKCPSYFRNSQICHCC^ (476)
A3.2 (F84)             --CCR--WPCPRQIDGEY-CGCCL# (477)
Bu3.5                  -RCCGEGLTCPRYWKNSQICACC^ (478)
Ca3.1                  --CCGPGGSCPVYFRDNFICGCC^ (479)
Cr3.1                  RKCCGKDGPCPKYFKDNFICGCC^ (480)
E3.1                   --CCS--WPCPRYSNGKLVCFCCL# (481)
M3.2                   --CCGPGGSCPVYFRDNFICGCC^ (482)
M3.3                   -MCCGESAPCPSYFRNSQICHCC^ (483)
M3.4                   ZKCCGPGGSCPVYFTDNFICGCC^ (484)
M3.5                   ZKCCGPGGSCPVYFRDNFICGCC^ (485)
S3.1                   ZKCCGEGSSCPKYFKNNFICGCC^ (486)
U001                   ZKCCS-GGSCPLYFRDRLICPCC^ (487)
U034                   ZKCCGPGASCPRYFKDNFICGCC^ (488)
Cn3.1                  -MCCGEGAPCPSYFRNSQICHCC^ (489)
```

TYPE 4

```
A3.3 (F83)             ZK--CCTGK---KGSCSGKACKNL-KCCS# (490)
A3.5 (Z488)            ZK--CCTGR---KGSCSGKACKNL-KCCS# (491)
Bu3.1                  VTDRCCK----GKREC-GRWCRDHSRCC# (492)
Bu3.1A                 VGDRCCK----GKRGC-GRWCRDHSRCC# (493)
Bu3.2                  VGERCCK---NGKRGC-GRWCRDHSRCC# (494)
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Bu3.3	IVDRCCN-KGNGKRGC-SRWCRDHSRCC# (495)
Bu3.4	VGLYCCRPKPNGQMMC-DRWCEKNSRCC# (496)
Ca3.2	-RD-CCTPP---KK-CKDRQCKPQ-RCCA# (497)
L3.1	GRD-CCTPP---RK-CRDRACKPQ-RCCG# (498)
L3.2	ZRL-CCGFP---KS-CRSRQCKPH-RCC# (499)
La3.2	-RD-CCTPP---KK-CRDRQCKPA-RCCG# (500)
La3.3	RPP-CCTYD---GS-CLKESCMRK-ACC# (501)
La3.3A	RPP-CCTYD---GS-CLKESCKRK-ACC# (502)
μ-GIIIA	-RD-CCTOO---KK-CKDRQCKOQ-RCCA# (503)
μ-GIIIB	-RD-CCTOO---RK-CKDRRCKOM-KCCA# (504)
μ-GIIIC	-RD-CCTOO---KK-CKDRRCKOL-KCCA# (505)
μ-PIIIA	ZRL-CCGFO---KS-CRSRQCKOH-RCC# (506)
M3.1	-RD-CCTPP---KK-CKDRQCKPQ-RCCA# (507)
Mr3.1	RGG-CCTPP---RK-CKDRACKPA-RCCGP# (508)
Nb3.2 (F582)	ZK--CCTGK---KGSCSGKACKNL-KCCS# (509)
Pr3.1 (Z500)	RGG-CCTPP---KK-CKDRACKPA-RCCGP# (510)
Pr3.2 (Z501)	-RG-CCTPP---RK-CKDRACKPA-RCCGP# (511)
R3.1	LOS-CCSLN---LRLCOVOACKRN-OCCT# (512)
R3.2	ZQR-CCTVK----RICOVOACRSK-OCCKS^ (513)
R3.3	RGG-CCTPP---RK-CKDRACKPA-RCCGP# (514)
Sm3.1	ZK--CCTGK---KGSCSGKACKNL-KCCS# (515)
T3.1	H-G-CCKGO---EG-CSSRECROQ-HCC# (516)
T3.2 (Y088)	H-G-CCEGP---KG-CSSRECRPQ-HCC# (517)
Wi3.1 (M548)	LPS-CCDFE----RLCVVPACIRH-QCCT# (518)

Type 5

Om3.2	CCKYGWTCLLGCTPCDC^ (519)
Om3.4	CCRYGWTCWLGCTPCGC^ (520)

Type 6

S3.2 (F352)	Z-NCCNGG-CSSKWCRDHARCC# (432)

EXAMPLE 3

Effect of Intrathecal Administration of μ-Conopeptides

[0087] Male C57 black mice (20-25g) are obtained from Charles River Laboratories. These mice and the animals are housed in a temperature controlled (23° ± 3° C) room with a 12 hour light-dark cycle with free access to food and water. All animals are euthanized in accordance with Public Health Service policies on the humane care of laboratory animals.

[0088] Intrathecal (it) drug injections are performed as described (Hylden and Wilcox, 1980). A μ-conopeptide or vehicle is administered in a volume of 5 μl. Duration of hind-limb paralysis is assessed. This experiment reveals that injection of μ-conopeptides into the intrathecal space of C57 black mice produced a paralysis of the animal. The animals in this experiment recovered fully.

EXAMPLE 4

Effect of μ-Conopeptides as a Local Anesthetic

[0089] Male Hartley guinea pigs (retired breeders) are obtained form Charles River Laboratories. The local anesthetic test is performed essentially as described (Bulbring and Wajda, 1945). On the day prior to test day, a patch on the back of the guinea pig is denuded of hair, first by shaving with electric clippers and subsequently with depilatory cream (Nair®). Depilatory cream is applied for five minutes and removed with a warm washcloth. The guinea pigs are dried and returned to their cages. On the following day, intradermal injections (0.1 ml vols) of lidocaine, bupivacaine, a μ-conopeptide or vehicle (0.5% cyclodextran) are made into the denuded patch. The injection produced a raised wheal on the surface of the skin which is circled with a felt-tipped pen. Typically, four injections are made on the back of each guinea pig. In some cases, guinea pigs are reused following at least one week of recovery and injecting into an unused portion of the skin. The stimulus consists of mild pin pricks (not hard enough to break the skin) with a 26G needle. The response is a localized skin twitch caused by contraction of cutaneous muscles. A unit test consisted of six uniform pin pricks, 3-5 seconds apart, within the injected area. Unit scores range from 0 (complete anesthesia) to 6 (no anesthesia). For potency experiments, the unit test is repeated at each site at five minute intervals for 30 minutes, and unit test scores summed (with 36 representing no anesthesia to 0 representing complete anesthesia. For duration experiments, unit tests are performed as described over the course of several hours to days.

[0090] μ-Conopeptides of the present invention produce a potent and long lasting local anesthetic effect in the intracutaneous wheal test in the guinea pig. As expected, bupivacaine has a slightly longer duration thatn lidocaine, consistent with clinical observations.

EXAMPLE 5

Muscle Relaxant Effect of μ-Conopeptides in Anesthetized Monkeys

[0091] μ-Conopeptides are dissolved 0.9 percent saline at a concentration of 2 mg/ml. Rhesus monkeys are anesthetized with halothane, nitrous oxide and oxygen. The maintenance concentration of halothane is 1.0%. Arterial and venous catheters are placed in the femoral vessels for drug administration and recording of the arterial pressure. Controlled ventilation is accomplished via an endotrachael tube. Twitch and tetanic contractions of the tibialis arterior muscle are elicited indirectly via the sciatic nerve. Recordings of arterial pressure electrocardiogram (lead I), heart rate, and muscle function are made simultaneously. Four to six animals received each listed compound. Four additional animals received succinylcholine chloride or d-tubocurarine chloride as controls. It is seen that the tested μ-conopeptides generally provide similar or better results than those seen for succinylcholine chloride or d-tubocurarine chloride.

EXAMPLE 6

In vivo Activity of μ-Conopeptides in Pain Models

[0092] The anti-pain activity of μ-conopeptides is shown in several animal models. These models include the nerve injury model (Chaplan, et al., 1997), the nocioceptive response to s.c. formalin injection in rats (Codene, 1993) and an NMDA-induced persistent pain model (Liu, et al., 1997). In each of these models it is seen that the μ-conopeptides and μ-conopeptides derivatives have analgesic properties.

[0093] More specifically, this study evaluates the effect of intrathecal administration of μ-conopeptides in mice models of nocioceptive and neuropathic pain. For nocioceptive pain, the effect of the μ-conopeptides is studied in two different tests of inflammatory pain. The first is the formalin test, ideal because it produces a relatively short-lived, but reliable pain behavior that is readily quantified. There are two phases of pain behavior, the second of which is presumed to result largely from formalin-evoked inflammation of the hind paw. A μ-conopeptide is administered 10 minutes prior to injection of formalin. The number of flinches and/or the duration of licking produced by the injection is monitored. Since the first phase is presumed to be due to direct activation of primary afferents, and thus less dependent on long term changes in the spinal cord, μ-conopeptides are presumed to have greatest effect on the magnitude of pain behavior in the second phase.

[0094] The mechanical and thermal thresholds in animals that received an injection of complete Freund's adjuvant into the hind paw are also studied. This produces a localized inflammation including swelling of the hind paw and a profound decrease in mechanical and thermal thresholds, that are detected within 24 hours after injection. The changes in thresholds in rats that receive μ-conopeptides are compared with those of rats that receive vehicle intrathecal injections.

[0095] An important issue is whether the drugs are effective when administered after the pain model has been established, or whether they are effective only if used as a pretreatment. Clearly, the clinical need is for drugs that are effective after the pain has developed. To address this issue, animals are studied in which μ-conopeptides are administered repeatedly, after the inflammation (CFA) or nerve injury has been established. In these experiments, a μ-conopeptide is injected daily by the intrathecal (i.t.) route. The mechanical and thermal thresholds (measured, respectively, with von Frey hairs in freely moving animals and with the Hargreave's test, also in freely moving animals) are repeated for a 2 to 4 week period after the injury is induced and the changes in pain measured monitored over time.

EXAMPLE 7

Effect of μ-Conotoxins in a Pain Model

[0096] Analgesic activity of μ-conotoxins is also tested in pain models as follows.

[0097] *Persistent pain (formalin test).* Intrathecal (it) drug injections are performed as described by Hylden and Wilcox (1980). An μ-conopeptide or vehicle is administered in a volume of 5 μl. Fifteen minutes after the i.t. injection, the right hindpaw is injected with 20 μl of 5% formalin. Animals are placed in clear plexiglass cylinders backed by mirrors to facilitate observation. Animals are closely observed for 2 minutes per 5 minute period, and the amount of time the animal spent licking the injected paw is recorded in this manner for a total of 45-50 minutes. Results are expressed as licking time in seconds per five minutes. At the end of the experiment, all animals are placed on an accelerating rotorod and the latency to first fall was recorded. μ-Conopeptides are found to be active in this model which is predictive of efficacy for treating neuropathic pain.

[0098] *Acute pain (tail-flick).* A μ-conopeptide or saline is administered intrathecally (i.t.) according to the method of Hylden and Wilcox (1980) in a constant volume of 5 μl. Mice are gently wrapped in a towel with the tail exposed. At various time-points following the i.t.

injection, the tail is dipped in a water bath maintained at 54° C. and the time to a vigorous tail withdrawal is recorded. If there is no withdrawal by 8 seconds, the tail is removed to avoid tissue damage.

[0099] *Neuropathic pain*. The partial sciatic nerve ligation model is used to assess the efficacy of μ-conopeptides in neuropathic pain. Nerve injury is produced according to the methods of Malmberg and Basbaum (1998). Animals are anesthetized with a ketamine/xylazine solution, the sciatic nerve is exposed and tightly ligated with 8-0 silk suture around 1/3 to ½ of the nerve. In sham-operated mice the nerve is exposed, but not ligated. Animals are allowed to recover for at least 1 week before testing is performed. On the testing day, mice are placed in plexiglass cylinders on a wire mesh frame and allowed to habituate for at least 60 minutes. Mechanical allodynia is assessed with calibrated von Frey filaments using the up-down method as described by Chaplan et al. (1994), and the 50% withdrawal threshold is calculated. Animals that did not respond to any of the filaments in the series are assigned a maximal value of 3.6 grams, which is the filament that typically lifted the hindlimb without bending, and corresponds to approximately 1/10 the animal's body weight.

[0100] The data obtained demonstrate that μ-conopeptides have potent analgesic properties in three commonly used models of pain: acute, persistent/inflammatory and neuropathic pain models.

EXAMPLE 8

Activity of μ-Conopeptide S3.2 on Neuronal Sodium Channels

[0101] μ-Conopeptide S3.2 was tested for activity on sodium channels as follows. S3.2 was administered to mice by intracerbroventricular (ICV) injection. Administration of S3.2 in this manner caused mice to show a spectrum of activity that is charcteristic of all sodium channel blockers, including rapid loss of righting reflex, coma-like inactivity and spastic uncontrolled limb movement. Following intrathecal (it) administration to mice, S3.2 causes rapid hindlimb paralysis that spreads to include the entire body over a course of 10-20 minutes followed by death, presumably due to respiratory paralysis. However, unlike classic μ-conopeptides, S3.2 has no significant activity following intravenous administration (iv) to mice. Classic μ-conopeptides, such as GIIIA and PIIIA, cause rapid paralysis and death following iv administration, indicating their activity at skeletal muscle sodium channels. To confirm the selectivity of S3.2, 80 nmol was administered iv to rats. The effect of S3.2 was measured on

skeletal muscle contraction, blood pressure and heart rate. S3.2 was found to have no effect on any of these parameters. Controls were performed using classical μ-conopeptides, including Sm3.1, Sm3.3 and Bu3.1 described herein, also administered iv at 80 nmol. These control peptides caused a dramatic decrease in skeletal muscle contractility, as well as a significant drop in systemic blood pressure. Thus, μ-conopeptide S3.2 suprisingly is selective for neuronal sodium channels. The most obvious difference between the S3.2 sequence and the sequences of these other peptides is a shortened first loop (the first loop between cysteine residues) which lacks a charged amino acid.

[0102] It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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